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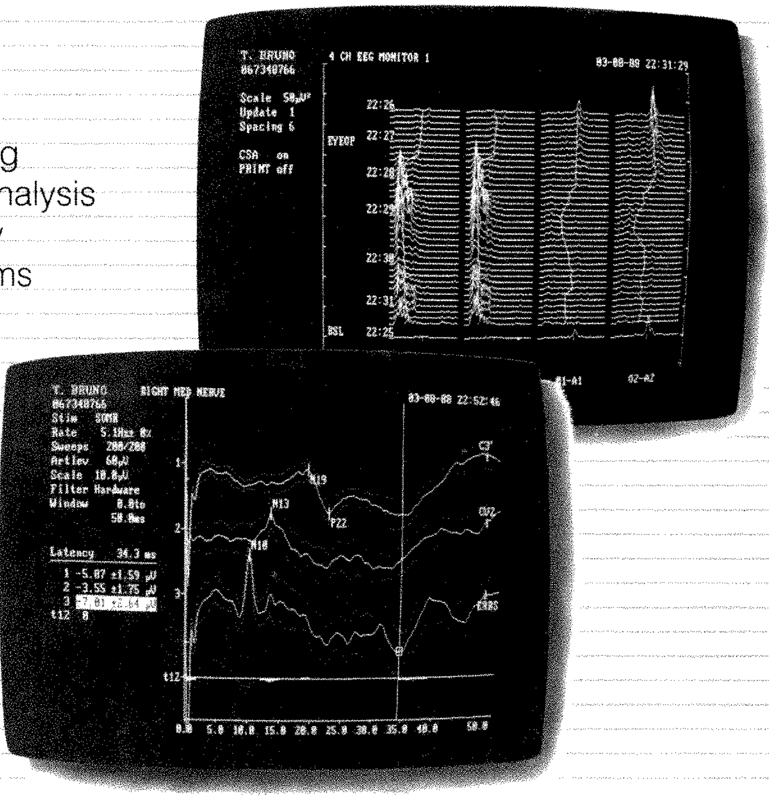

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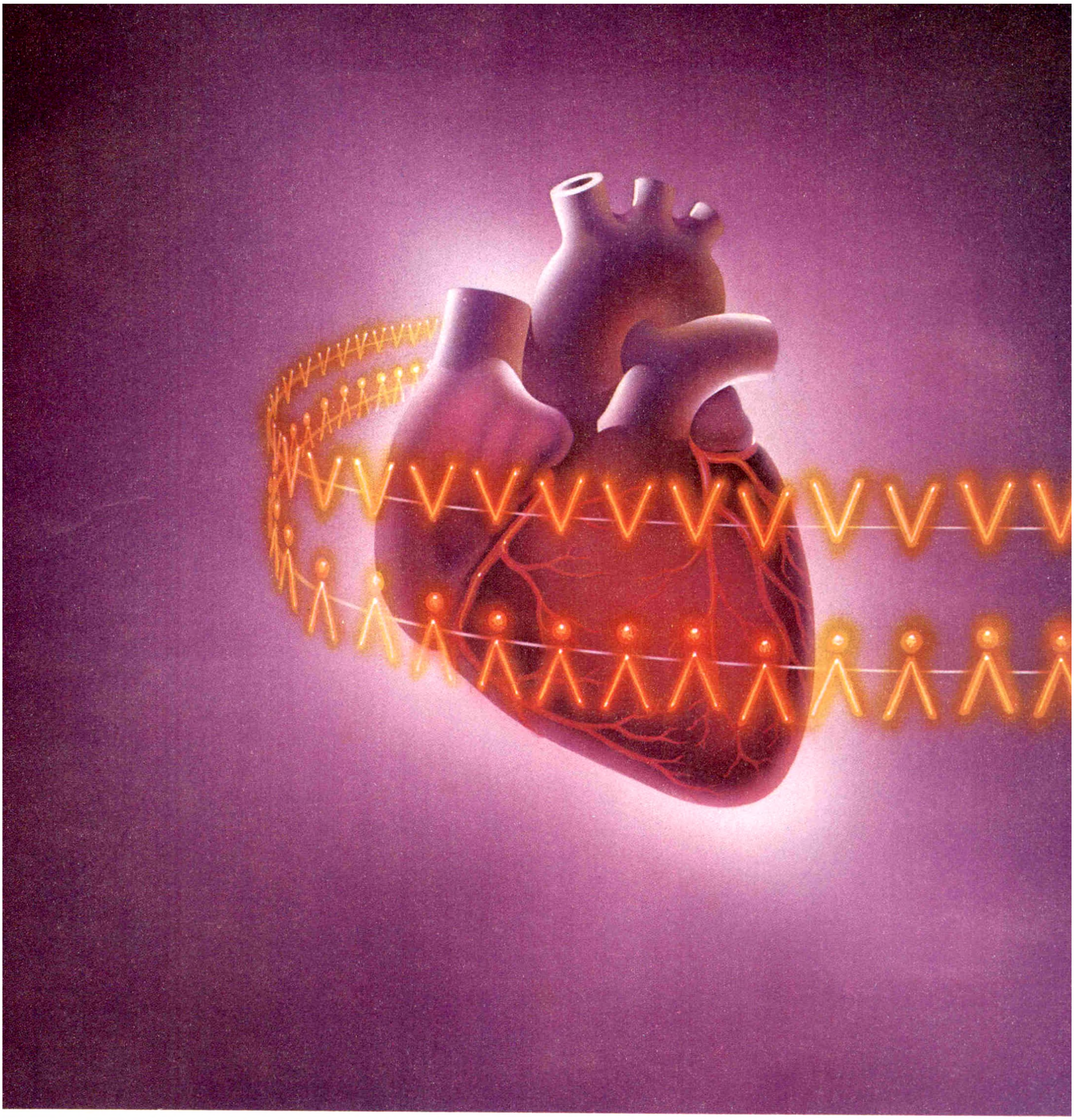

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Editorial

Spinal Analgesia with Morphine and Clonidine

Luke M. Kitahata, MD, PhD

Key Words: ANALGESICS—morphine, clonidine. SYMPATHETIC NERVOUS SYSTEM—pharmacology, clonidine.

Spinal opioid analgesia utilizing opioid analgesics has been one of the major developments during the past decade in the management of acute and chronic pain. The relief of pain is due to the interaction of the opioid injected epidurally or intrathecally with a specific opioid receptor in the spinal cord. The result is zones of segmental analgesia without the loss of motor function or loss of other sensory modalities, such as touch sensation.

The direct demonstration of opioid receptors (1–3) and the isolation of endogenous opioid-like peptides from the central nervous system (4,5) were all due to the application of the receptor theory. These developments have had a great impact on the research on pain and pain modulation. In the late 1960's and early 1970's, neurophysiological and neuropharmacological studies demonstrated suppressive effects of various general anesthetics and opioid analgesics on the nociceptive neurons of the dorsal horn of the spinal cord (6–11). Coinciding with the discovery of opioid receptors and the isolation of endogenous opioid-like peptides, the results of these neurophysiological and neuropharmacological studies led to the demonstration of anti-nociception in behaving animals (12) and eventually to human application of spinal opioid analgesia (13).

As with any new technique, spinal opioid analgesia has side effects which include respiratory depression, development of tolerance, urinary retention, pruritis, and somnolence. Among those complications, respiratory depression following spinal opioid application is potentially the most dangerous. It is a life-threatening complication that limits the wide clinical usage of this new technique of pain control, especially in an out-patient setting. There have been various attempts to minimize this complication: For instance, 1) the use of more lipid-soluble agents to penetrate the spinal cord more readily and, therefore, to decrease the amount of opioid present in the cerebrospinal fluids that can ascend cephalad to depress brainstem respiratory neurons; 2) simultaneous administration of naloxone; and 3) positioning the patient to prevent or decrease cephalad movement of the opioid agonist in cerebrospinal fluids. Each of these has, however, additional disadvantages. Highly lipid-soluble agents have shorter durations of action; simultaneous naloxone administration may be associated with cardiovascular instability and loss of analgesic effect; and keeping the patient in the head-up position is uncomfortable and may contribute to cardiovascular instability. One way to solve this problem is to combine adrenoreceptor agonists with opioids in order to decrease the effective doses of opioid agonists.

Since the early demonstration by Weber (14) and the application of epinephrine to the spinal cord would produce an attenuation of the thermally-evoked withdrawal response in the cat, alpha agonists were shown to potentiate the effects of systemically-administered morphine (15,16). More recent studies have shown that intrathecally-administered alpha-2 agonists significantly shift the opioid dose-response curve to the left when they were co-administered intrathecally (17–20). This combined effect is due to the co-activation of the two sets of receptors. Since the clearance of morphine from the intrathecal space is relatively slow, the clearance of the opiate drug may not be significantly altered by the presence of alpha-2 agonists. Thus, it is unlikely that the combined analgesic effect is caused by an alteration in clearance of either drug.

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Ossipov et al. report in this issue on anti-nociceptive interactions between alpha-2 adrenergic and opiate agonists at the spinal level in rodents (21). Their findings for the most part confirm the work done by previous workers. They combined three important aspects of the investigation, namely, studies on potentiation, antagonism and tolerance. They conclude that the spinal administration of combinations of an alpha-2 agonist and an opiate may be expected to produce greater analgesia than either alone, thereby reducing the dose requirements and delaying the onset of tolerance. They have further postulated that the administration of an alpha-2 agonist in an individual tolerant to opiates may not produce the degree of analgesia expected in a naive individual since a partial cross-tolerance may occur.

It is reasonable to assume that the use of multiple receptor concepts will decrease the effective dosage of opioid analgesics thereby lessening or preventing the complications mentioned above. In addition to the combination of opiates and alpha-adrenoreceptor agonists, there are other selective classes of receptor agonists operative at the spinal cord level producing a powerful elevation in the nociceptive threshold. They include neurotensin (22–24), acetylcholine (25), serotonin (26), and GABA (27). These other systems may be as effective as the combination of opiate and alpha-adrenoreceptor agonist. The goal is, therefore, to determine the best combination of these agonists for use in humans. This requires that, first, the exquisitely sensitive neurophysiologic and neuropharmacologic studies of spinal cord function that have paved the way for development of these new techniques of pain control must be undertaken to assay the efficacy of combinations of anti-nociceptive agents administered spinally. In addition, appropriate histological studies must be conducted in animals before human studies are done with a variety of receptor-selective, intrathecal, or epidural agents in high concentration being applied within the vicinity of the human spinal cord, as the administration of these drugs into the spinal space may potentially be hazardous.

The basic understanding of spinal cord pharmacology has led to significant advances in the management of acute and chronic pain. The understanding of the complex pharmacology of spinal cord function promises significant advances and offers a good possibility for rational advances in pain management. The interaction among the various classes of agonists operative in the spinal cord is an important field of study for the advancement of spinal analgesia. More effective and safer methods of pain control through spinal analgesia may well be seen in the future as more work is done using the multiple spinal cord receptor concept.

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Antinociceptive Interactions Between Alpha$_2$-Adrenergic and Opiate Agonists at the Spinal Level in Rodents

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OSSIPOV MH, SUAREZ LJ, SPAULDING TC. Antinociceptive interactions between alpha$_2$ adrenergic and opiate agonists at the spinal level in rodents. Anesth Analg 1989;68:194–200.

This study was undertaken to evaluate the antinociceptive interactions of α_2 adrenergic and opiate receptors at the spinal level. Morphine and clonidine were administered intrathecally (i.t.) by lumbar puncture to rats either alone or in the presence of either i.t. yohimbine, an α_2 antagonist, or systemic naloxone, an opioid antagonist. The effect of tolerance to systematically administered morphine on responses to i.t. morphine and clonidine was examined in mice. Antinociception was determined by observing the response to a clamp applied to the tail (Haffner test) in mice and by the tail-flick test in rats; log dose-response curves for antinociception were generated for morphine, clonidine, and each drug combination. Morphine and clonidine both produced dose-dependent antinociception when given i.t. in both species. The i.t. administration of yohimbine attenuated the antinociceptive effect of both clonidine and morphine, but naloxone attenuated only the response to morphine. Further, a sub-analgetic dose of i.t. clonidine potentiated the effect of i.t. morphine. In morphine-tolerant mice, i.t. morphine was not efficacious whereas clonidine retained full efficacy, although potency was slightly diminished. Thus, it appears that α_2 adrenoceptor-mediated antinociception is independent of opiate receptor mechanisms. Clinical use of intrathecal combinations of α_2 adrenergic and opiate receptor agonists to increase analgesia and use of intrathecal α_2 agonists for pain relief in patients tolerant to opiates might deserve evaluation.

Key Words: ANALGESICS, MORPHINE—clonidine. RECEPTORS, OPIOID—adrenergic. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine.

It is well established that morphine produces its antinociceptive effect by an action at opiate receptors located at both supraspinal and spinal sites (1–3). Moreover, the combined effect of morphine administered supraspinally and spinally is synergistic (4). It is also widely accepted that systematically and intrathecally administered clonidine, an α_2 adrenergic agonist, produces an antinociceptive effect (5–9), and it is suggested that α_2-mediated antinociception is solely due to a spinal site of action (10,11). Several investigators have reported that the tail flick reflex, a spinally mediated response to nociception, remains active in mice (10) and rats (11,12) with transections of the thoracic spinal cord and that this reflex is attenuated by i.t. and systemic morphine. Further, the antinociceptive potency of clonidine administered systemically to mice (10) or rats (11) is not altered by transection of the spinal cord, whereas that of systemic morphine is diminished (10,12). Although the tail flick reflex is a spinal phenomenon, it is under a descending modulatory influence from supraspinal sites (11). Because opiates may inhibit this spinal reflex both supraspinally, by activating descending modulatory influences, and spinally, by directly inhibiting nociceptive input (2,4), then removal of the descending inhibitory influence by spinal transection effectively attenuates the supraspinal component of the antinociceptive effect of morphine, leaving only the spinal component intact (10,12). Thus, the potency of morphine is effectively reduced. In contrast, because removal of descending inhibitory pathways (by spinal transection) does not diminish the potency of clonidine with regard to inhibition of the nociceptive tail flick reflex, then one may surmise that the site of action of clonidine-mediated antinociception lies entirely within the spinal reflex arch (10,11).

Additional evidence that suggests that supraspinal α_2 adrenoceptors are not active in modulating spinal nociceptive reflexes include studies that show that the administration of clonidine or its analog ST-91, also an α_2 agonist, to supraspinal sites associated

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with antinociception either failed to elicit antinociceptive effects or produced hyperalgesia (13–15).

The antinociceptive effect of supraspinally administered morphine is dependent on spinal serotonergic and noradrenergic nerve terminals (16,17), and spinal adrenergic-produced antinociception is mediated by α_2 adrenergic receptors (18–21). Thus, there appears to be a dependence on α_2 adrenergic receptors for opiate-mediated antinociception. This premise has been the basis for a number of experiments indicating that morphine-produced antinociception is increased by the administration of α_2 agonists and diminished by α_2 adrenergic antagonists (14,22). The clinical potential of a combination of morphine and clonidine is attractive in that reduced doses of opiates may be used to produce analgesia, thus delaying the onset of tolerance.

If α_2 adrenergic mediated antinociception is independent of opiate receptor activation, then one would expect that a spinally administered α_2 adrenergic agonist would produce analgesia in the morphine tolerant individual. Clinical evidence exists to show that such treatment may be effective (23).

Because morphine produces its effect at either spinal and supraspinal sites, whereas that of clonidine is apparently limited to a spinal site of action, the site of interaction between opiates and α_2 adrenergic receptors in producing antinociception remains unclear. The present study was undertaken to examine the interaction between opiate receptor and α_2 adrenoceptor mediated antinociception at the spinal level.

Methods

Male Swiss-Webster mice (10 to 20 g) and male Sprague-Dawley rats (50 to 75 g) were used in all experiments. No animal was used in more than one experiment. The experiments were approved by our Animal Care and Use Committee.

Rat Tail-Flick

The rat tail-flick test, a modification of that described by D'Amour and Smith (24), was performed by placing the tail of a rat under a focused (2 mm × 4 mm) radiant heat source (Analgesiameter, IITC, Landing, NJ) that was activated simultaneously with a timer. When the radiant heat stimulus became painful, the rat flicked its tail aside, uncovering a photocell and shutting off both lamp and timer. Control tail-flick latencies were determined to the nearest 0.1 second for each rat twice before i.t. drug injection. Post-treatment tail-flick latencies were determined 5 minutes after i.t. clonidine and 10 minutes after i.t. morphine. This timing represented the time of peak effect determined from preliminary experiments. A maximum exposure (cut-off latency) of 10 seconds was used to prevent tissue damage. The effect observed at each dose was used in the construction of dose-response curves.

Mouse Haffner Assay

The mouse Haffner assay was originally described by Haffner (25) in 1929 and later modified by Takagi et al. (26). The assay is performed by applying a serrefine artery clip that delivers a force equivalent to a weight of 400 g applied to the base of the tail of a mouse. A nociceptive response is defined by a biting of the clip or surrounding area by the mouse. Control response latencies were determined in our study once for each mouse before i.t. injection. Post-treatment biting latencies were determined 1, 2.5, 5, and 10 minutes after injection. A cut-off latency of 15 seconds was used. The maximal effect observed at each dose was used in generating the log dose-response curves.

Injection Technique

The intrathecal injections were performed according to the method of Hylden and Wilcox (27). The animal was held firmly by the pelvic girdle. A 30 g needle, attached to a 25 μl Hamilton syringe was inserted into the tissue on one side of the L5 or L6 spinous process at an angle of about 20°. The needle was advanced into the groove between the spinous and transverse processes and then moved forward into the intervertebral space at an angle of about 10°. About 0.5 cm of the needle was then in the vertebral column. Correct placement of needle was indicated by a reflexive arching of the tail in response to the advancement of the needle. Studies where cresyl violet dye was injected in this manner and spinal cord sections subsequently examined showed that this technique reliably produces an i.t. injection (J. Vaught, personal communication). This injection method was used in both mice and rats. Drugs were dissolved in saline solution or water and administered in a volume of 5 μl.

Antagonism Studies

To examine the effect of yohimbine, an α_2 antagonist, on intrathecally administered morphine and clonidine, 30 μg of yohimbine were administered i.t. 5 minutes prior to i.t. morphine or 10 minutes prior to i.t. clonidine. This timing assured that the tail flick tests would be performed 15 minutes after i.t. yohimbine and at the time of peak effect of all drugs involved. Several doses of agonists were used to construct dose response curves in the presence of yohimbine. These dose-response curves were then compared with the effects observed with the agonist alone.

Naloxone, 1 mg/kg, was administered by intraperitoneal (i.p.) injection 10 minutes prior to i.t. morphine or 15 minutes prior to i.t. clonidine. This timing assured that the tail-flick tests would be performed 20 minutes after i.p. naloxone and at the time of peak effect of all drugs involved. As with yohimbine, dose-response curves for i.t. administered morphine and clonidine were compared with those obtained in the absence of naloxone.

In a separate study, a pharmacologically ineffective dose of clonidine (25 μg) was administered intrathecally 5 minutes after the intrathecal injection of morphine. The tail-flick test was performed at the time of peak effect for both drugs, which was 5 minutes for clonidine and 10 minutes for morphine. The difference between the dose-response curve for morphine in the presence of clonidine and that for morphine alone was analyzed for its statistical significance.

Tolerance to Morphine

In additional studies, mice were made tolerant to morphine over a 3-day dosing regimen with use of a modification of a design described by Saelens et al. (28) in which mice were injected s.c. with 50 mg/kg of morphine at 8:00 a.m., 100 mg/kg at 12:00 noon, and 200 mg/kg at 4:00 p.m. on the first day and 200 mg/kg of morphine at 8:00 a.m. and at 4:00 p.m. on the following day. On the third day, the mice were injected with 200 mg/kg at 8:00 a.m. and received i.t. doses of the challenge drugs at 4:00 p.m. A separate group of 48 control animals received saline solution injections at each of the time periods during which morphine was injected in the other groups.

Statistical Analysis

The degree of antinociception was defined as the percent maximum possible effect (% MPE) in both the mouse Haffner assay and rat tail-flick tests and was calculated as

$$\frac{(\text{post-treatment latency} - \text{control})}{(\text{cut-off latency} - \text{control})} \times 100.$$

Table 1. $^*A_{50}$ Values of Intrathecal Morphine and Clonidine in the Rat Tail-Flick Tests

	A_{50} (95% Confidence Intervals; Slope of the Dose-Response Curve)	R	N
Morphine	9.0 μg(2.6-30.5;48)	0.90	24
Morphine + naloxone	>100 μg		18
Morphine + yohimbine	38 μg(4.1-360;86)	0.95	18
Morphine + clonidine	0.37 μg(0.26-0.51;47)	0.99	30
Clonidine	46 μg(4.5-469;96)	0.95	18
Clonidine + naloxone	52 μg(27.4-100;102)	0.93	18
Clonidine + yohimbine	123 μg(77.5-194.5;52)	0.98	24

$^*A_{50}$ is the amount of drug producing 50% of the maximal possible analgesic effect (i.e., 100% effect) of the drug calculated as described in the text. Ascending doses of morphine were administered intrathecally (i.t.) either alone, 10 min after naloxone (1 mg/kg i.p.), 5 min after yohimbine (30μg i.t.), or 5 min prior to clonidine (25 μg i.t.). Ascending doses of clonidine were administered i.t. either alone, 15 min after naloxone (1 mg/kg i.p.), or 5 min after yohimbine (30 μg i.t.). R = the regression coefficient of the fitted dose-response line; N = number of animals per treatment.

The cut-off latencies were 10 seconds and 15 seconds for the rat tail-flick and mouse Haffner tests, respectively. The % MPE was determined for each dose at each time period measured, and the largest value obtained with each dose was plotted against the log dose. A regression line was calculated by a method of least squares, as were the A_{50} values (dose that produced 50% MPE) and the 95% confidence limits. The slopes of each regression line with the 95% confidence limits and Student's *t* values were calculated and used when testing for parallelism. All statistical calculations were performed by computer programs described by Tallarida and Murray (29).

Results

Interaction Between Opiates and α_2 Adrenergic Agonists

Intrathecal clonidine and morphine both produced dose-dependent antinociception in the rat. After i.t. administration, the A_{50} of clonidine in the rat tail-flick test was 46 μg and that of morphine was 9 μg (Table 1). The dose-response curves were not statistically parallel. After pretreatment with an i.t. injection of 30 μg of yohimbine, the antinociceptive potencies of both morphine and clonidine administered intrathecally were reduced. Yohimbine pretreatment caused a parallel 4-fold shift to the right in the dose-response curve for morphine (Fig. 1) and significantly ($P \leq 0.05$) increased the i.t. A_{50} of morphine to 38 μg (Table 1). Pretreatment with yohimbine also produced a parallel shift to the right of the dose-response curve for clonidine (Fig. 2) and tripled the i.t. A_{50} of clonidine to 123 μg (Table 1). This decrease in potency failed to achieve statistical significance, but this

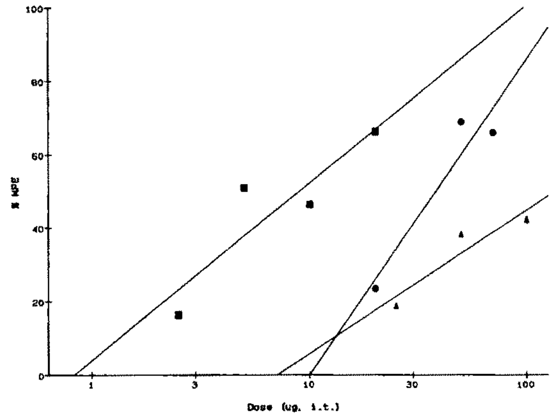

Figure 1. The dose-related increases in tail-flick latency in the rat after intrathecal (i.t.) injection of morphine are represented as % MPE (see text). Morphine was administered either alone (■), 5 min after 30 μg of yohimbine i.t. (●), or 10 min after 1 mg/kg of naloxone i.p. (▲). Response latencies were determined as the peak effect observed 10 min after the i.t. injection of morphine. The regression lines for all treatments shown did not deviate from parallelism.

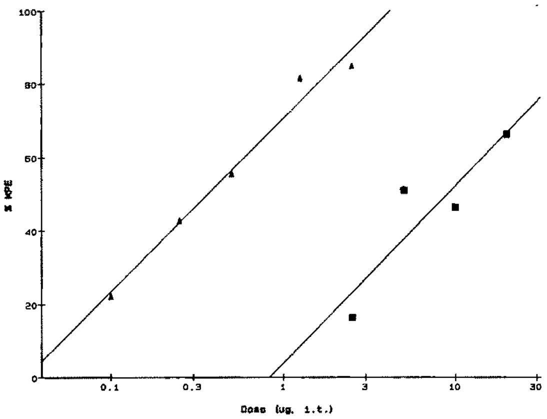

Figure 3. The dose-related increases in tail-flick latency in the rat after intrathecal (i.t.) injection of morphine are represented as % MPE (see text). Morphine was administered either alone (■) or 5 min prior to 25 μg of clonidine i.t. (▲), which represented a subanalgetic dose. The response latencies were determined as the peak effect observed 10 min after the injection of morphine. The regression lines for both treatments were statistically parallel.

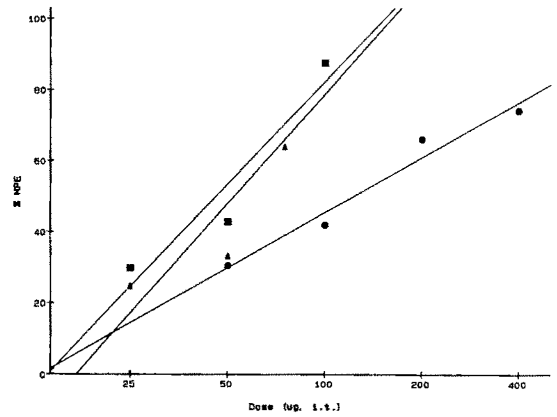

Figure 2. The dose-related increases in tail-flick latency in the rat after intrathecal (i.t.) injection of clonidine are represented as % MPE (see text). Clonidine was administered either alone (■), 10 min after 30 μg of yohimbine i.t. (●), or 15 min after 1 mg/kg of naloxone i.p. (▲). Response latencies were determined as the peak effect observed 5 min after the injection of clonidine. The regression lines for all treatments shown did not deviate from parallelism.

may be due to the rather large confidence interval calculated for the dose response curve for clonidine alone (Table 1). In the presence of i.t. yohimbine, 30 μg, the response to 100 μg i.t. of clonidine in the tail-flick test was 42% MPE, which is significantly ($P \leq 0.05$) less than the response of 87% MPE obtained with the same dose of i.t. clonidine alone.

The systemic administration of naloxone (1 mg/kg, i.p.) completely abolished the analgetic activity of morphine up to 100 μg i.t. in the rat (Fig. 1). The allodynia produced by this high dose of morphine was not prevented by the administration of naloxone. In contrast to morphine, the potency of i.t. clonidine was not altered by naloxone pretreatment, and the dose-response curve for i.t. clonidine plus naloxone was parallel to that of clonidine alone (Fig. 2). The A_{50} value of clonidine in the rat tail-flick test after naloxone injection was 52 μg, only slightly higher than the A_{50} of 46 μg for clonidine in rats not exposed to naloxone (Table 1); these A_{50} values are not significantly ($P > 0.05$) different. The high dose (1 mg/kg i.p.) of naloxone was administered to ensure that antagonism of any opiate-receptor mediated event would occur.

The i.t. injection of a subanalgetic dose of clonidine (25 μg) produced parallel 24-fold shift to the left of the morphine dose-response curve generated in the rat tail-flick test (Fig. 3). The A_{50} of morphine in the presence of clonidine was 0.37 μg, which is significantly ($P \leq 0.05$) less than the A_{50} of 9 μg for morphine alone (Table 1).

Tolerance to Morphine

The i.t. administration of morphine to mice receiving systemic injections of saline solution over 3 days produced dose-dependent antinociception in the Haffner test and an A_{50} of 0.44 μg (Table 2). In mice made tolerant to morphine by 3 days of systemic injections of morphine, not saline solution, the i.t. administration of up to 10 μg of morphine did not produce any significant increase in response latency (Fig. 4). Allodynia, however, was seen after i.t. administration of the highest i.t. dose of morphine.

The development of tolerance to morphine injected systemically produced a slight decrease in the

Table 2. *A_{50} Values of Intrathecal Morphine and Clonidine in the Mouse Haffner Assay in Morphine Tolerant Mice

	A_{50} (95% Confidence Intervals; Slope of the Dose-Response Curve)	R	N
Morphine-naive	0.44 μg(0.14-1.37;73)	0.92	24
Morphine-tolerant	>10 μg		12
Clonidine-naive	13 μg(9.3-19.6;83)	0.99	24
Clonidine-tolerant	34 μg(15.6-76.4;145)	0.98	18

*As described in Table 1 and text. Mice were made tolerant to morphine over a 3 day dosing regimen; control mice received saline solution injections at similar time intervals. Increasing doses of morphine and clonidine were administered i.t. to groups of tolerant and naive mice. R = the regression coefficient of the fitted dose-response line; N = number of animals per treatment.

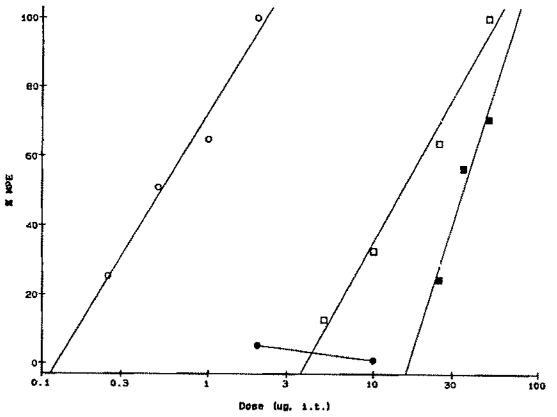

Figure 4. The dose-related changes in the mouse Haffner test for morphine and clonidine in naive and morphine-tolerant mice are shown as % MPE (see text). Morphine (circles) or clonidine (squares) was administered i.t. to naive (open symbols) or morphine-tolerant (solid symbols) mice. Response latencies were determined as the peak effect observed within 15 min of the injection. The regression lines for clonidine in naive and tolerant mice were statistically parallel.

antinociceptive potency of i.t. administered clonidine. Pretreatment with morphine caused a 3-fold parallel shift to the right in the dose-response curve for clonidine (Fig. 4), and significantly ($P \leq 0.05$) increased the A_{50} of clonidine from 13 μg to 35 μg (Table 2). For both clonidine and morphine, the time to peak effect was 1 minute.

Discussion

Yaksh et al. (30) have described a hyperesthesia (or allodynia) characterized by violent scratching and biting responses to stimuli that are normally not nociceptive in response to the intrathecal administration of large doses of morphine or its metabolites. This response was not present after the administration of opiates that were not structurally related to morphine. Moreover, the hyperesthesia was not opiate-receptor mediated. In our study, we found that high i.t. doses of morphine produced an allodynia in rats that received a high systemic dose of naloxone or in mice tolerant to morphine, thus supporting the lack of opiate-receptor involvement in this effect of morphine.

It is well established that α_2 adrenergic receptor activation is important to antinociception produced by morphine administered systemically or supraspinally (16,18). Systemic administration of the α_2 antagonist yohimbine attenuates the antinociceptive effect of an opiate administered either systemically or supraspinally and α_2 antagonists given intrathecally decrease the antinociceptive effect of intracranial morphine (14,18,22). The results reported here extend observations of the dependence of antinociception on spinal α_2 adrenergic receptor stimulation to morphine administered intrathecally. Clearly, the antinociceptive effect of i.t. morphine was attenuated by spinal yohimbine. In contrast, the administration of naloxone failed to attenuate the antinociceptive effect of i.t. clonidine, although that of morphine was entirely abolished, as is expected (2). This result is similar to that reported after systemically administered morphine (22). A recent report by Solomon and Gebhart (31) also shows that in an anesthetized rat preparation, the effect of i.t. morphine is attenuated by yohimbine, but that the effect of i.t. clonidine is not affected by naloxone. Such results clearly indicate that, even at the spinal level, the action of α_2 adrenoceptors is probably distal to that of the opiate receptors with regard to the inhibition of responses to noxious input, and that α_2 mediated antinociception may occur independently of opiate receptor activation.

The significant shift to the left of the dose-response curve for intrathecally administered morphine elicited by an inactive dose of spinal clonidine suggests a potentiation of morphine by clonidine. These results confirm data obtained from electrophysiologic studies showing that i.t. clonidine potentiated the ability of i.t. morphine to reduce dorsal horn unit responses to afferent noxious stimuli (32,33). Other studies (6,22) have demonstrated a potentiation of the antinociceptive effect of systemically administered clonidine by systemically administered morphine, and of intrathecal morphine by systemic clonidine (34). Our results are in agreement with these findings and further confirm a positive interaction between opiates and α_2 adrenergic agonists at the spinal level.

Fielding et al. (22) have shown that mice made tolerant to morphine by pellet implantation retain the antinociceptive effect of clonidine administered systemically. Our data extend these observations in mice by showing that tolerance to systemically administered morphine completely abolishes the antinociceptive effect of intrathecally administered morphine and significantly reduces the antinociceptive potency of intrathecally administered clonidine. Cross-tolerance is not complete, however, because i.t. clonidine remained fully effective, although less potent, in the morphine tolerant animals. Recently, rats made tolerant to clonidine by repeated bolus injection of clonidine became tolerant to both morphine and clonidine, but tolerance produced by morphine was not investigated in that study (31). In a contrasting report, however, Stevens et al. (35) indicated that ST-91 and morphine are not symmetrically cross-tolerant when tolerance is produced by i.t. infusion of either ST-91 or morphine over a period of 7 days. In their study, the chronic i.t. infusion of ST-91 increased the dose requirements of i.t. bolus ST-91 but not of morphine, whereas tolerance produced by intrathecally infused morphine decreased the antinociceptive potency of morphine and of ST-91, although to a lesser extent.

The results of this study further illustrates the positive interaction between α_2 adrenoceptors and opiate receptors at the level of the spinal cord. Together with the observations cited previously, our data allow us to suggest that the α_2 adrenoceptor acts at a site distal to the opiate receptor with regard to modulation of responses to nociception. We propose that morphine activates opiate receptors that subsequently cause the activation of α_2 adrenergic receptor-mediated mechanisms inhibiting nociceptive input at the spinal level. Our results support the observations that opiate-mediated antinociception depends at least in part on spinal noradrenergic mechanisms (16,17) and reinforce the interpretation of Zemlan et al. (11), who suggested that the α_2 receptor acts "downstream" from the opiate receptor in the spinal modulation of antinociception. This proposed mechanism does not preclude a direct role of the opiate receptor at the spinal site in addition to one dependent on an intact α_2 adrenergic system. It is possible that morphine also acts on opiate receptors located on noci-responsive neurons that contain α_2 receptors as well. Indeed, morphine-mediated antinociception is not completely abolished by either the presence of an α_2 antagonist or development of tolerance to an α_2 agonist (35).

If clonidine were to act directly through the opiate receptor or morphine through the α_2, then the interaction between morphine and clonidine would be additive rather than synergistic; additionally, the action of clonidine would be reversed by naloxone or the action of morphine would not be completely abolished in morphine tolerant mice. The evidence presented here do not support such a mechanism for either clonidine or morphine.

In conclusion, the spinal administration of combinations of an α_2 agonist and an opiate may be expected to produce greater analgesia than either alone, thereby reducing the dose requirements and delaying the onset of tolerance. Moreover, the administration of an α_2 agonist in an individual tolerant to opiates may not produce the degree of analgesia expected in a naive individual because a partial cross-tolerance may occur, but would be effective at higher dosage levels.

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General Anesthesia During Percutaneous Transluminary Coronary Angioplasty for Acute Myocardial Infarction:

Results of a Randomized Controlled Clinical Trial

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Acutely ill patients with myocardial infarction may require immediate cardiac catheterization and coronary angioplasty to achieve myocardial reperfusion. To determine the feasibility of using general anesthesia under these circumstances, a randomized clinical trial was performed. Of 50 patients, 25 received anesthesia and 25 received intravenous sedation. There were transient increases in heart rate and blood pressure after tracheal intubation in the anesthetized patients, followed by significant and sustained decreases below baseline values once steady state anesthesia was attained. Arterial oxygenation was significantly improved in anesthetized patients. There were no serious complications due to anesthesia, but the small sample size limited the power of the study to detect differences in morbidity or mortality. Patients strongly preferred anesthesia. These results show that general anesthesia is feasible in patients undergoing interventional cardiac catheterization during acute myocardial infarction,.when pain, anxiety or agitation do not respond adequately to conventional measures.

Key Words: ANESTHESIA, cardiovascular. HEART, MYOCARDIAL INFARCTION—angioplasty.

Acute transmural myocardial infarction is caused by sudden occlusion of a major coronary artery, and recent studies have shown that jeopardized myocardium can be salvaged by prompt recanalization of the occluded vessel (1). Coronary angiography within 4 to 6 hours of the onset of pain can identify the occluded vessel and may be used to re-establish perfusion by intracoronary administration of thrombolytic agents or by coronary angioplasty. During this procedure, introducers are inserted into the femoral artery and vein in order to enable right and left heart catheterization. A pacing catheter is inserted into the right ventricle. The left ventricle is catheterized for contrast ventriculography to evaluate left ventricular global contractility and regional wall motion. Subsequently, the coronary arteries are selectively catheterized to visualize the right and left coronary systems in multiple planes.

After the infarct related vessel has been identified, a thrombolytic agent (streptokinase, urokinase or tPA) is infused into this vessel or a guide wire is passed across the stenosis followed by a balloon catheter. Once the balloon is in the correct position, it is inflated with a pressure of 5–10 atm, for 60–120 seconds. Multiple dilations may be necessary before satisfactory dilation is achieved. Preliminary data suggest that percutaneous transluminary coronary

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angioplasty leads to a significant improvement in the outcome of patients with myocardial infarction (1).

Acute myocardial infarction is associated with significant pain, anxiety, increased serum catecholamines levels (2), and reduced arterial oxygenation. These derangements may accelerate irreversible tissue injury, because myocardial oxygen demands are increased by elevations in heart rate, blood pressure and contractility, while myocardial oxygen delivery may be further compromised by decreased arterial oxygenation (2,3). The stress of immediate cardiac catheterization may actually exacerbate these adverse factors in some patients. Conversely, the degree of pain, anxiety, agitation and respiratory impairment add to the difficulty and risk of performing cardiac catheterization and coronary angioplasty in a critically ill patient. General anesthesia offers several potential advantages when used during interventional cardiac catheterization. General anesthesia completely eliminates the pain and anxiety associated with both the myocardial infarction and the procedure. Tracheal intubation protects the airway and may prevent pulmonary aspiration in non-fasting patients, many of whom develop nausea from the contrast material, drug treatment, or the underlying myocardial infarction (4). Controlled ventilation may improve arterial oxygenation, and elimination of patient movement facilitates rapid performance of the procedure. Finally, general anesthetics may aid myocardial salvage by exerting a direct protective effect on ischemic myocardium (5), possibly due to changes in intracellular calcium fluxes (6,7).

Despite these potential advantages, general anesthesia has been avoided during the acute phase of myocardial infarction except when cardiac surgery is indicated. The reluctance to administer anesthesia may be due to the relatively high rates of cardiovascular complications in patients anesthetized in the six months after myocardial infarction and the recognition that the rate of complications is higher the more recent the myocardial infarction (8). However, advances in anesthetic technique and extensive experience in patients with failed angioplasty with acute ischemia and those with unstable angina undergoing coronary artery bypass grafting suggest that anesthesia might be feasible even in the setting of an acute myocardial infarction. We tested this approach in a pilot study of six patients, and found changes in hemodynamics, oxygenation, and patient satisfaction (9). On the basis of this preliminary experience, we initiated a randomized controlled clinical trial to compare general anesthesia with intravenous sedation during interventional cardiac catheterization for acute myocardial infarction.

Methods

Criteria for entry into the study included: 1) prolonged chest pain consistent with myocardial ischemia and/or infarction, 2) transfer to the interventional cardiac catheterization laboratory for emergency cardiac catheterization within 6 hours of the onset of pain, and 3) ST-segment elevations of 0.2 mV or greater in two or more leads of a 12-lead electrocardiogram. Exclusion criteria were: 1) participation in a concurrent protocol studying tissue plasminogen activator, 2) clinical evidence of shock, or 3) hypoventilation or hypoxemia warranting intubation.

After obtaining written informed consent, patients were randomly assigned to Group A, which received general anesthesia, or Group S, which received intravenous sedation with local infiltration anesthesia at the site of insertion of catheters. All patients were given lidocaine 225 mg in divided injections followed by a continuous infusion at a rate of 2 mg/min. At the start of the catheterization procedure they were also given 10,000 units of heparin. Forty-eight of the 50 patients received 1.5 million units of intravenous streptokinase prior to catheterization.

Patients in both groups had a 20-gauge radial arterial catheter inserted for hemodynamic monitoring and blood sampling. Subsequently, patients in group A were given 100% oxygen by mask followed by 100–150 μg of fentanyl as well as vecuronium 2 mg intravenously. Rapid sequence induction of anesthesia was then performed using etomidate 0.3 mg/kg followed by succinylcholine 1.5 mg/kg and droperidol up to 5 mg intravenously. Tracheal intubation was performed while cricoid pressure was applied. An esophageal stethoscope, a nasogastric tube and a urinary bladder catheter were inserted. The adequacy of neuromuscular blockade was monitored and anesthesia was maintained using 50% N_2O/O_2 and 0–0.5% enflurane. Enflurane was not started until after ventriculography to avoid possible depression of left ventricular contractility. At the end of the procedure, neuromuscular block was reversed in Group A patients with neostigmine 2.5 mg and glycopyrrolate 0.6 mg intravenously. Return of consciousness and neuromuscular function was followed immediately by tracheal extubation.

The patients in Group S received 40% inspired oxygen by face mask, plus morphine 0.5 mg and diazepam 0–10 mg intravenously as needed. An anesthesiologist determined the need for and dosage of intravenous sedatives.

Cannulation of the right femoral artery and vein was performed for placement of a transvenous right ventricular pacing catheter, left ventriculography and coronary arteriography. Coronary angioplasty was performed using standard methods for patients with significant (≥75%) narrowing of luminal diameter in the infarcted vessel. Balloon inflation up to nine atmospheres for 60–120 sec. was used for coronary arterial dilatation.

Heart rate, systolic, diastolic and mean systemic arterial pressures were recorded immediately after insertion of the radial arterial catheter, 1 minute after tracheal intubation in the anesthetized group or at a comparable time in Group S (11 minutes after baseline), five minutes after intubation (15 minutes after baseline in Group S), immediately prior to left ventriculography, at the end of coronary arteriography, at the initial reperfusion, at the end of the procedure, at tracheal extubation (end of the procedure plus 5 minutes in Group S) and at 5 minutes after extubation (end of procedure plus 10 minutes in Group S). Arterial blood samples were drawn for determination of pH, pO_2, pCO_2 and base excess at baseline, intubation plus 5 minutes (15 minutes after baseline in Group S), prior to ventriculography, at initial reperfusion, at the end of the procedure, and at arrival in the cardiac care unit.

All patients were followed daily in the cardiac care unit, and data concerning their hospital course were collected by a research nurse. To evaluate patient perceptions of the procedure, 3 to 5 days after the procedure all patients were asked to complete a self-administered questionnaire which included a modified version of the RAND Health Insurance Study psychologic status scales (10).

Data were analyzed using the SAS statistical software. Discrete data were compared with χ^2 and Fisher's exact tests and continuous data were compared using the Wilcoxon rank sum test.

Results

Characteristics of the 50 randomized patients are presented in Table 1. There were slightly more women in the sedated group and more patients with peripheral vascular disease in the anesthetized group, but these differences were not statistically significant. Otherwise, the patient groups were well balanced. Roughly half the patients had anterior and half had inferior myocardial infarctions (Table 2). The number of diseased vessels was comparable in the two groups; one-vessel disease was present in 13 Group A patients and in 11 Group S patients, two-vessel disease was present in seven Group A patients and eight Group S patients, and three-vessel disease was present in three Group A patients and six Group S patients. One patient in Group A had no significant coronary lesion after intravenous streptokinase and another had an unsuccessful catheterization due to severe peripheral vascular disease. Median left ventricular ejection fraction was 40% in group A and 46% in Group S (p = NS).

Most patients in the study had presented initially to an outside hospital and were transferred by helicopter for interventional catheterization. The median interval from onset of pain to administration of thrombolytic therapy was 221 minutes in Group A and 174 minutes in Group S (p = NS). The median time of arrival in the interventional catheterization laboratory was 339 minutes after onset of continuous chest pain in Group A, and 315 minutes in Group S (p = NS). The procedure was not delayed as a result of anesthesia: median time from arrival at the laboratory to initial ventriculography was 31 minutes in Group A and 35 minutes in Group S (p = NS). Sustained reperfusion of the infarct related artery was achieved in 88% of patients in Group A and in 92% of patients in Group S (p = NS).

Hemodynamic values and arterial blood gas tensions were comparable at the time of baseline measurements (Fig. 1). Anesthetic induction did not

Table 1. Demographic Data

Patient Characteristics	General Anesthesia	Sedation
Sex	21 M 4 F	16 M 9 F
Hypertension	14	13
Diabetes mellitus	3	6
Family history of coronary artery disease	10	9
Smoking history	17	15
Pulmonary disease	6	6
Peripheral vascular disease	4	0
Cerebrovascular disease	4	3
Previous myocardial infarction	7	4
Prior congestive heart failure	0	0
Pulmonary Rales	4	5
S_3 gallop	23	23
Mitral regurgitation	2	4
Neurologic findings	0	1

Table 2. Location of Coronary Lesions

	General Anesthesia	Sedation
Left anterior descending	10	15
Left circumflex	2	1
Right coronary artery	11	9
None	1	0
Unknown	1	0

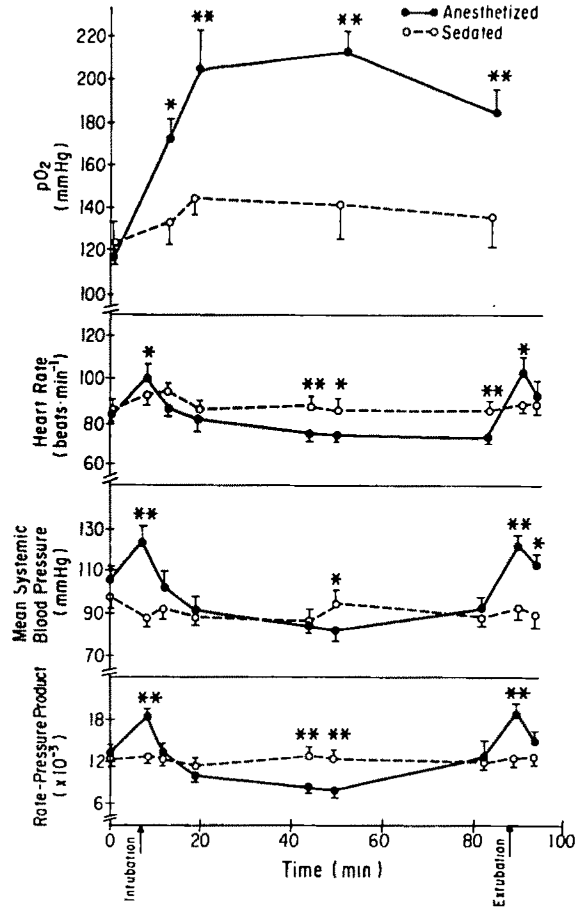

Figure 1. Hemodynamic and oxygenation data throughout the procedure in the anesthetized and sedated patients. The vertical axis includes arterial pO_2, heart rate, mean blood pressure, and rate-pressure product. The horizontal axis indicates the time in minutes after baseline measurements. The times of intubation (8 minutes) and extubation (91 minutes) are indicated by arrows. *—$p < 0.05$; **—$p < 0.005$ in intergroup comparisons.

change hemodynamic parameters, but tracheal intubation briefly increased systemic arterial pressure from 107.5 to 123.8 mm Hg and heart rate to 100.7 from 86.2. However, once steady-state anesthesia had been attained, heart rate and blood pressure throughout the procedure were decreased significantly compared with baseline and compared with sedated patients ($p < 0.005$ and $p < 0.05$, respectively, Fig. 1). One minute after extubation, systemic pressure increased significantly to 122 from 92.9 and the heart rate to 105.6 from 73.5.

Arterial oxygenation data are also summarized in Figure 1. Prior to intubation, levels of arterial pO_2 were comparable in the two groups of patients. Subsequently, the pO_2 in Group A was significantly higher than in Group S ($p < 0.01$). The increase in pO_2 was associated with a significant increase in arterial oxygen saturation ($p < 0.01$). Furthermore, five of the patients in Group S had a pO_2 of less than 70 at some point during the procedure, while none of the 25 patients in Group A had a pO_2 of less than 82 at any time during the procedure. There were no significant differences in arterial pH or pCO_2 between the groups.

There were no significant differences in the rate of complications in the study groups. Table 3 summarizes data concerning the patients who died during hospitalization (three in Group A, two in Group S) and those with complications during the procedure. None of these deaths or complications appeared related to anesthesia or sedation. In the cardiac care unit, four patients in each group developed pulmonary edema and five in each group developed ventricular tachycardia. Three patients in Group A developed post-anesthetic agitation that required sedation. Two patients in Group A and one in Group S developed radiographic findings suggestive of pneumonia, but none had fever or clinical evidence of pulmonary infection.

Several days after the procedure, there were no significant differences between the groups in levels of anxiety, depression, positive wellbeing, or loss of behavioral/emotional control. Table 4 summarizes the response to the question "If you had to have another procedure to open a blood vessel in the heart, would you rather be put to sleep (get general anesthesia) or be awake (get local anesthesia)?" The vast majority (88%) of patients who had general anesthesia wanted it again if they ever needed another interventional cardiac catheterization. In contrast, only 33% of patients who had intravenous sedation wanted it again if they ever needed another interventional cardiac catheterization, while 38% expressed a preference for general anesthesia.

Discussion

This study demonstrates that general anesthesia may be used as an adjunct to interventional cardiac catheterization during acute myocardial infarction. General anesthesia has not been compared to sedation in patients in the midst of an acute infarction previously. Anesthesia has immediate and obvious effects on patient comfort and, not surprisingly, anesthesia was strongly preferred by patients. Furthermore, the improved oxygenation and hemodynamic observed during anesthesia may favorably affect the balance of myocardial oxygen supply and demand. However, we were unable to document a protective effect of anesthesia on myocardial salvage.

Despite previous studies demonstrating the benefits of parenteral analgesia and sedation (11–13), anesthesia has generally been viewed as particularly

Table 3. Hospital Deaths and Laboratory Complications

Group	Age, Sex	MI Location	No Vessels	EF	Comment
S	58M	Ant	3	44	PTCA failure, reperfusion cath placed, emergency CABG. Died 2 days post-CABG with electromechanical dissociation.
S	75F	Ant	1	39	Give intravenous streptokinase, 1.5 million units, successful PTCA. Died day 3 of intracranial bleed.
A	72M	Inf	3	59	Acute MI during lymph node biopsy, 95% left main, no PTCA, no streptokinase. Urgent CABG 7 days later, died 2 months post-CABG of multi-organ failure.
A	53M	Ant	1	37	Give IV streptokinase, vessel open with 50% lesion, no PTCA done. PT taken to CCU in good condition, 4 hours later developed dyspnea, and then electromechanical dissociation, and could not be resuscitated.
A	74M	Inf	3	44	Complete heart block and hypotension responsive to dopamine on presentation. Successful PTCA. 2 episodes ventricular tachycardia. Remained intubated post-procedure due to hypoventilation. Progressive hypotension unresponsive to pressors and intra-aortic balloon pump. Died 1 day post-MI.
A	62M	Ant	1	37	Successful PTCA, but with recurrent ventricular fibrillation after anesthesia reversed. Repeat angiogram showed reoccluded vessel, not responsive to PTCA. Reperfusion catheter placed, emergency CABG.
A	58M	Inf	2	22	Transient hypotension responsive to dopamine. Transient complete heart block.

PTCA, Percutaneous Transluminary Coronary Angioplasty
CABG, Coronary Artery Bypass Grafting
CCU, Coronary Care Unit
MI, Myocardial Infarction
EF, Ejection Fraction
ANT, Anterior
INF, Inferior

Table 4. Patient Preferences

	General Anesthesia (N = 22)	Sedation (N = 21)
Prefers General Anesthesia	19 (86%)	8 (38%)
Prefers Intravenous Sedation	2 (9%)	7 (33%)
No Preference	1 (5%)	6 (29%)

$p < 0.003$

dangerous during acute myocardial infarction. There are several reasons for this concern, chiefly the potential for deleterious effects on the heart, such as increasing arrhythmogenicity or depressing myocardial contractility. Newer inhalation agents and modern intravenous anesthetic agents have fewer effects and are safer for patients with myocardial ischemia (14,15). Also, considerable experience has been accumulated with patients undergoing coronary bypass surgery for unstable coronary syndromes including myocardial infarction. Surgical patients cannot, however, be randomized to sedation or general anesthesia for this reperfusion procedure and, thus, this protocol provides a unique opportunity to study both general anesthesia and sedation in patients with acute ischemia. When patients are anesthetized to permit myocardial revascularization, as in the present study, the risk of anesthesia is probably reduced when ischemia is abolished by the coronary revascularization, making it impossible to transfer the present results to patients who do not receive a revascularization procedure. Thus the data do apply to patients who will require a surgical revascularization procedure (coronary artery bypass surgery) and reflect the safety of at least one anesthetic approach.

The changes observed in our anesthetized patients (Figure 1) are consistent with improved oxygen delivery and reduced oxygen consumption. Of note, however, heart rate and blood pressure were significantly increased for a short period of time by the stresses of intubation and extubation, probably as a result of the relatively light level of anesthesia. There were subsequent prolonged decreases in heart rate and blood pressure, however, and the average heart rate-blood pressure product, throughout the procedure, an approximate measure of myocardial oxygen demand, was significantly reduced by anesthesia. Others, such as Maroko et al. (16), have shown that these interventions increase myocardial salvage in acute animal experiments. Perhaps the use of short acting intravenous beta-blockers, such as esmolol, at the time of intubation and extubation would blunt these changes and improve the hemodynamic profile during anesthesia further protecting the ischemic heart from increased oxygen consumption and exposure to circulating catecholamines.

The effects of general anesthesia on outcome remain speculative, but two lines of evidence suggest that they may be beneficial. First, animal research with halogenated inhalation anesthetics has demonstrated an association between an anesthetic-induced reduction in myocardial oxygen requirements and myocardial protection from ischemic injury. When compared with the awake state, anesthetized animals with lower heart rate and mean arterial pressure have a decrease in arrhythmias, mortality and infarct size after coronary artery ligation (14,15). A selective increase in oxygen supply relative to demand in ischemic myocardium has also been demonstrated with inhalation anesthetics (17,18). Second, acute beta-adrenergic receptor blockade in patients during acute myocardial infarction appears to reduce mortality and infarct size (19). To the extent that this effect is mediated by the reduction in heart rate and blood pressure, other agents with similar hemodynamic effects could confer similar benefits. Thus, the cardiac effects of anesthesia may actually be beneficial as an adjunct to myocardial reperfusion therapy.

There is also some laboratory evidence to suggest that anesthesia may favorably affect myocardial salvage, independent of any possible effects on myocardial oxygen supply or demand. A proposed mechanism for the myocardial protective effects of inhalation anesthetics is their effect on myocardial calcium. An anesthetic concentration of halothane reduces the rate of calcium uptake in spontaneously beating rat atria, and calcium influx across the myocardial plasma-membrane is decreased in the presence of general anesthetics (6). Furthermore, calcium-triggered calcium release in isolated sarcoplasmic reticulum is significantly increased by clinical concentrations of general anesthetics (7). A decreased calcium content in myocardial cells may retard the onset of irreversible injury, which may be mediated in part by calcium loading of mitochondria.

One aspect of our study design deserves particular comment. Both the anesthetized and sedated patients in this study were closely monitored and managed by an experienced cardiac anesthetist. In particular, the anesthetist managed hemodynamics, arrhythmias, sedation, analgesia and oxygenation, freeing the cardiologist to concentrate on performing the procedure. This division of responsibility contrasts with the usual practice in which the cardiologist is responsible for both performing the procedure and managing the critically ill patient. The close attention and frequent intervention by the anesthetist in the control patients probably led to optimal sedation. A third control group managed in the usual fashion by the cardiologist would be necessary to investigate formally whether the presence of anesthesia standby improves patient outcome during interventional cardiac catheterization for acute MI. We suspect patient outcomes may be optimal by having one individual assume primary responsibility for patient management and another assume primary responsibility for performing the cardiological procedure. The former could be performed by a second cardiologist as well as by an anesthetist, and, clearly, the addition of anesthesia standby as a routine would add considerably to the cost of the procedure, and further study would be required to justify this additional cost.

There are several important limitations to this study. First, the sample size of 50 patients was relatively small. Although we did not observe any significant increase in adverse effects in the anesthesia group, it would take a very large study to establish this confidently. For instance, it would take a sample size of 1864 patients to have 80% power to detect an increase in mortality from 8% to 12% at the conventional significance level of 0.05. Similarly, any beneficial effects of anesthesia on myocardial salvage or outcome could not be established without a large study involving thousands of patients. The overall mortality rate in this study was 10% (5/50), which is comparable to the 12% mortality rate in the larger population of patients undergoing interventional cardiac catheterization for acute myocardial infarction (20). Second, while institution of general anesthesia did not substantially delay the onset of the interventional procedure in this research study, in practice longer delays may be encountered with potentially deleterious effects on myocardial salvage. Third, anesthesia during interventional cardiac catheterization eliminates the patient's ability to report on the recurrence of chest pain, so that early reocclusions may be missed. To decrease this possibility, reversal of neuromuscular blockade and extubation should be performed in the catheterization laboratory. It has been our experience that the peak of reocclusion of infarct-related vessels occurs at 24 hours. The electrocardiogram and pulmonary artery wedge pressure should be monitored closely in the cardiac care unit as early signs of reocclusion. Pain during the procedure is not a reliable sign to follow since all patients have pain and the adequacy of reperfusion is determined by repeat angiography and EKG criteria. In the case of late reocclusion the patient will be awake and pain could then be used as an additional indication of reocclusion. Finally, anesthesia in this study was administered by anesthetists with considerable experience in cardiac anesthesia: caution must be used in applying these methods in hospitals that have cardiac catheterization facilities but relatively low volumes of cardiac surgery or anesthetists untrained in cardiac anesthesia.

This study demonstrates that general anesthesia can be used as an adjunct to interventional cardiac catheterization for acute myocardial infarction. These findings support the use of anesthesia in patients whose pain, anxiety or agitation does not respond adequately to conventional measures.

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Dose-Response Relation and Time Course of Action of Pipecuronium Bromide in Humans Anesthetized with Nitrous Oxide and Isoflurane, Halothane, or Droperidol and Fentanyl

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WIERDA JMKH, RICHARDSON FJ, AGOSTON S. Dose-response relation and time course of action of pipecuronium bromide in humans anesthetized with nitrous oxide and isoflurane, halothane, or droperidol and fentanyl. Anesth Analg 1989;68:208–13.

The dose-response relation of pipecuronium bromide, the time course of its neuromuscular blocking effects, and the reversibility of the residual block by neostigmine and edrophonium have been investigated in patients undergoing various types of anesthesia. The estimated doses of pipecuronium required for 95% depression of the twitch height were 44.6, 46.9, and 48.7 $\mu g \cdot kg^{-1}$ during anesthesia with nitrous oxide (65%) and isoflurane (group 1), halothane (group 2), or droperidol/fentanyl (group 3), respectively. The potentiating effects of the volatile anesthetics were reflected by the significant prolongation of the duration of both initial (50.0 ± 4.3, 36.0 ± 3.3, and 29.0 ± 2.0 minutes) and maintenance doses (56.0 ± 2.5, 49.5 ± 3.3, and 41.2 ± 1.6 minutes) of pipecuronium during anesthesia with nitrous oxide and isoflurane, halothane, or droperidol/fentanyl, respectively. Both edrophonium chloride (0.5 $mg \cdot kg^{-1}$) and neostigmine methylsulphate (40 $\mu g \cdot kg^{-1}$) promptly reversed the residual block induced by pipecuronium. No side effects attributable to pipecuronium were seen in this study.

Key Words: ANESTHETICS, INTRAVENOUS—fentanyl, droperidol. ANESTHETICS, VOLATILE—halothane, isoflurane. NEUROMUSCULAR RELAXANTS, PIPECURONIUM.

Pipecuronium bromide (hereafter referred to as pipecuronium) is a new, long-acting, neuromuscular blocking agent with a chemical structure similar to that of pancuronium. The pharmacologic profile of pipecuronium has been extensively studied by Kárpáti and Biró (1), and the first clinical results were reported by Boros et al. (2,3) and Tassonyi et al. (4). Based on results from these studies, it appears that the administration of pipecuronium is not followed by either release of histamine or circulatory side effects, such as tachycardia and/or hypotension. The present report describes the results of clinical trials designed to evaluate potency, time course of action, and reversibility of the pipecuronium-induced neuromuscular blockade in patients having anesthesia with nitrous oxide and either isoflurane, halothane, or droperidol and fentanyl.

Patients, Materials, and Methods

Patients

This open clinical trial was approved by the Medical Ethical Committee of the University Hospital of Groningen. Sixty-three ASA physical status 1 and 2 patients, 20 to 60 years of age, scheduled for elective gynecologic or orthopedic operations, gave their consent to participate in the study. Excluded from the study were patients with known kidney, liver, or neuromuscular disorders or those taking any medication known to interfere with the action of neuromuscular blocking agents.

Anesthesia

All patients were premedicated with oral diazepam (0.15 $mg \cdot kg^{-1}$) given approximately 60 minutes be-

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fore the expected induction of anesthesia. Depending on the anesthesia technique employed, the patients were randomly assigned into three groups to receive anesthesia with nitrous oxide and either isoflurane, halothane, or droperidol/fentanyl. In patients receiving isoflurane (n = 22) or halothane (n = 21), anesthesia was induced with 3–5 mg·kg^{-1} thiopental intravenously (IV). Thereafter, the patient's lungs were ventilated using a face mask with nitrous oxide/oxygen (in a ratio of 2 to 1) to which either isoflurane or halothane was added in gradually increasing inspired concentrations up to 3% isoflurane (Fortec® vaporizer Cyprane, Keighley, U.K.) or 2% halothane (Fluotec® vaporizer Cyprane, Keighley, U.K.) prior to tracheal intubation. Thereafter, anesthesia was maintained with 0.8 to 1.5% isoflurane or 0.5 to 1.0% halothane, according to the need of the patient until the end of the surgical procedure.

In patients having neurolept anesthesia (n = 20), anesthesia was induced with droperidol (0.15–0.3 mg·kg^{-1} IV), followed 4 to 6 minutes later with fentanyl (3 to 9 μg·kg^{-1} IV) and, immediately before intubation, thiopental (2 to 3 mg·kg^{-1} IV) was injected. During induction, the patients lungs were ventilated with 35% oxygen in nitrous oxide.

The induction of anesthesia was followed by the dose-response part of the study, after which the administration of pipecuronium was completed to a total of 50 μg·kg^{-1}. After 2 minutes, tracheal intubation was performed, preceded by topical administration of 4% lidocaine.

Monitoring

In all patients the electrocardiogram, blood pressure, heart rate, and end-tidal CO_2 (Capnograph Mark II, Gould-Godard, Cleveland, Ohio) were monitored during anesthesia. Esophageal temperature was maintained at ±37°C by means of a warming mattress and warmed inspired anesthetic gases.

Isometric measurement of the indirectly evoked twitch height was started after induction of anesthesia. A Grass S88 peripheral nerve stimulator (Grass Instruments, Quincy, Massachusetts) was used, and supramaximal bipolar pulses of 0.2-ms duration were administered to the ulnar nerve at the wrist via surface electrodes at the rate of 0.1 Hz (twitch response) or 2.0 Hz (train-of-four [TOF] stimulation, when appropriate). The resultant force of thumb adduction was quantitated with a force displacement transducer (UC3, Gould-Statham, Oxnard, California), isolated signal amplifier (Anesthesiology Department, Groningen University, The Netherlands), baseline stabilizer (Anesthesiology Department, Groningen University, The Netherlands), and a Brush 220 recorder (Gould, Cleveland, Ohio) at a continuously monitored stable resting tension of the adductor pollicis muscle of 200 to 300 g.

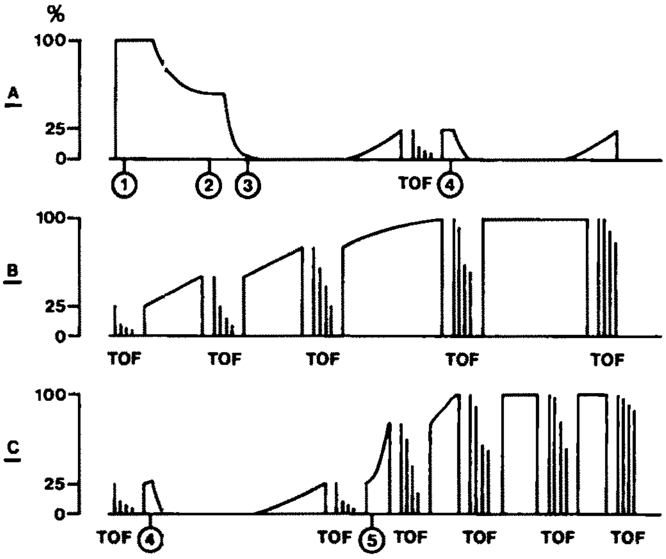

Figure 1. Experimental procedure (schematic presentation). Vertical scale: control twitch height (%), horizontal scales: time. Upper (A) and middle (B) panels represent the dose-response part of the study with *spontaneous* recovery of the pipecuronium-induced neuromuscular blockade. Upper (A) and lower (C) panels demonstrate the procedure when reversal of the residual block was *induced* by either neostigmine or edrophonium. At 1 × μg·kg^{-1} (selected initial dose), at 2 a supplementary dose up to a total of 50 μg·kg^{-1} (total initial dose) of pipecuronium was administered, at 3 intubation was performed and at 4 a maintenance dose 25 μg·kg^{-1} of pipecuronium, at 5 neostigmine or edrophonium was injected. Percentage train-of-four (TOF) was measured at 25%, 50%, 75%, and 100% recovery of the twitch height (upper and middle panel A + B) or 2, 5, 8, and 10 mins after the administration of the reversal agent when recovery was induced (lower panel C).

Experimental Procedure

The design of the experiment is illustrated in Figure 1. In the first part of each experiment, the dose-response relation of pipecuronium was studied, whereas in the remaining part, the time course of action and reversibility of the total initial dose and the subsequent maintenance doses were investigated.

After induction of anesthesia, 10 to 15 minutes were allowed for stabilization of anesthesia and of the twitch response, before one of the selected doses (20, 30, 40, or 50 μg·kg^{-1}) was administered at random. This dose was dissolved in 10 ml of saline solution and administered over 10 seconds. With each selected initial dose, at least five patients were studied. Once the maximum effect of the selected initial dose was reached (that is, when no further decrease in evoked twitch height occurred in response to three consecutive stimuli), a supplementary dose was injected. The size of the supplementary dose was chosen so that together with the selected initial dose a total of 50 $\mu g \cdot kg^{-1}$ was administered to all patients. This is approximately the ED95 dose for pipecuronium reported by other investigators (5–8).

The onset time, clinical duration, duration of maintenance doses, and recovery index were recorded. Onset time was defined as the time from injection of the selected initial dose to maximum effect. Patients with <5% or >95% block were excluded. Clinical duration was defined as the time from injection of the full dose (50 $\mu g \cdot kg^{-1}$) to 25% recovery of the twitch height.

At this point, depending on the expected duration of the operation, a maintenance dose of 25 $\mu g \cdot kg^{-1}$ was injected, although (if possible) no further muscle relaxant was given and spontaneous recovery of the twitch response was permitted to occur. Train-of-four tests were then performed at 25, 50, 75, and 100% recovery of the twitch height, and the rate of spontaneous recovery was calculated. However, when muscle relaxation was still required, a second and further maintenance doses were administered always at the point of 25% recovery after the previous maintenance dose. In these patients, the time interval between maintenance doses was taken as the duration of the maintenance dose. In all patients in whom spontaneous recovery of the neuromuscular transmission was permitted to occur, the recovery index (time from 25 to 75% recovery of the twitch height) was also recorded.

All other patients were given either neostigmine methylsulphate (40 $\mu g \cdot kg^{-1}$) or edrophonium chloride (0.5 $mg \cdot kg^{-1}$) to reverse the residual block at the 25% recovery point following the initial (total) or last maintenance dose of pipecuronium. Methylatropine nitrate (7 $\mu g \cdot kg^{-1}$) was given either together with neostigmine (injected over 30 seconds, IV) or alone over 15 seconds immediately prior to edrophonium, which was given over 30 seconds. Just before and 2, 5, 8, and 10 minutes after the injection of the reversal agent, TOF tests were performed. If at 10 minutes the percentage of the TOF had not reached 70%—a level generally regarded as being indicative of a degree of recovery, sufficient for spontaneous ventilation—a second dose (1/2 of the first dose) of the same reversal agent was given and the TOF responses recorded again at the same intervals.

By the experimental procedure just described, data could be generated for:

1. construction of the dose-response curves by recording the maximum effect of the selected initial doses,
2. measurement of the time course of action and reversibility of the effect of pipecuronium in all patients, and
3. quantitation of the effects of the inhalational anesthetics either on the magnitude, time course, or reversibility of the pipecuronium-induced neuromuscular blockade.

Statistical Analysis

Dose-response curves were constructed by plotting $\log_{10}$ dose of pipecuronium against percent twitch depression. From these curves, ED50 and ED95 values were estimated for pipecuronium during the various anesthetic techniques. For further statistical analysis, depending on the character of the data and differences in variation coefficients, Students *t* test (two-tailed), one way analysis of variance (for comparisons involving three treatment groups), and Fisher's least significant difference (LSD) procedure for pairwise comparisons were employed. All values are expressed as mean ± SEM. Statistical significance was inferred if $P < 0.05$.

Results

Dose-Response Relation

A significant linear relation was found when the logarithmic doses of pipecuronium were plotted against percent depression of twitch height during nitrous oxide and isoflurane, halothane, or droperidol/fentanyl. As is shown in Figure 2, with increasing doses of pipecuronium, a corresponding increase of depression of twitch height was observed.

The estimated regression equations based on the individual data and correlation coefficients were $y = 134 \times -126$, $y = 143 \times -144$, $y = 179 \times -207$, and 0.71, 0.79 and 0.84 in isoflurane, halothane, and droperidol/fentanyl groups, respectively [$x = \log$ (dose) and $y = \%$ block]. From the calculated regression lines, the ED50 and ED95 doses were determined (Table 1).

Time Course of Neuromuscular Blocking Effects (mean ± SEM)

After 50 $\mu g \cdot kg^{-1}$ of pipecuronium as a single bolus injection, twitch height was depressed 98.0 ± 1.3,

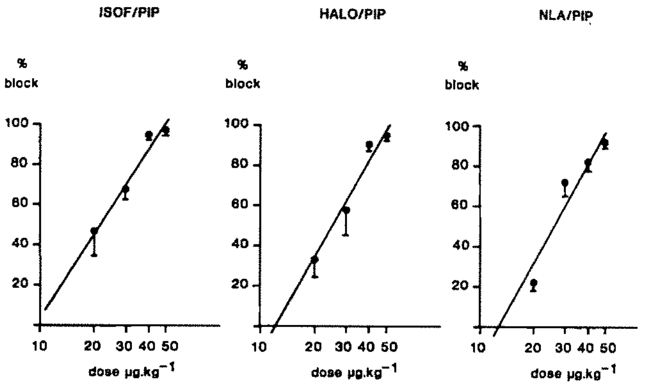

Figure 2. Dose-response relationship of pipecuronium following induction in patients receiving anesthesia with nitrous oxide and isoflurane (ISOF/PIP), halothane (HALO/PIP) or droperidol/fentanyl (NLA/PIP) [Mean ± SEM]. Vertical scale: % depression of the twitch height. Horizontal scale (logarithmic): dose ($\mu g \cdot kg^{-1}$).

Table 1. Effective Dose (ED) Estimates for Pipecuronium Bromide Derived from the Dose-Response Curves

	Anesthetic Group*			
	Isoflurane (n = 22)	Halothane (n = 21)	Drop/Fent (n = 20)	*P*
ED50 dose ($\mu g \cdot kg^{-1}$)	20.6	22.7	27.3	NS
ED95 dose ($\mu g \cdot kg^{-1}$)	44.6	46.9	48.7	NS

*Patients in each anesthetic group were also receiving 65% nitrous oxide.
Abbreviations: Drop/Fent, droperidol and fentanyl, NS = not significant.

96.8 ± 1.2, and 93.0 ± 2.2% in patients receiving nitrous oxide and isoflurane, halothane, and droperidol/fentanyl, respectively (P = NS). The time to maximum effect or 95% block for these groups were 5.4 ± 1.1, 5.5 ± 0.5, and 6.3 ± 0.5 minutes, respectively. The onset times (6.4 ± 0.4, 6.7 ± 0.5, and 6.7 ± 0.4 minutes, respectively) were not different and appeared to be independent of the size of the dose. The TOF responses and recovery index during spontaneous recovery (51.0 ± 8.5, 37.0 ± 6.5, and 31.0 ± 3.1 minutes, respectively) were not different. However, with respect to the recovery index, the latter numbers were not statistically different mainly because of the small numbers of patients who were allowed to recover spontaneously from their neuromuscular block.

The clinical duration (injection − 25% recovery time) of the total 50 $\mu g \cdot kg^{-1}$ dose was 50.0 ± 4.3, 36.0 ± 3.3, and 29.0 ± 2.0 minutes in patients receiving nitrous oxide and isoflurane, halothane, or droperidol and fentanyl, respectively, and was statistically different among all three groups. The duration of maintenance doses averaged 56.0 ± 2.5 minutes for the isoflurane group, 49.5 ± 3.3 minutes for the halothane group, and 41.2 ± 1.6 minutes for the droperidol/fentanyl group, the differences being significant only between values obtained in the groups receiving isoflurane and droperidol/fentanyl.

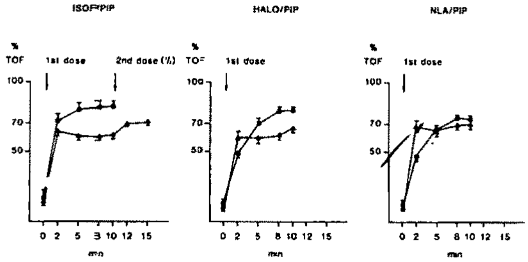

Figure 3. Percentage train-of-four recovery (TOF)—vertical scale—vs time (min)—horizontal scale—following edrophonium chloride (▲) 0.5 $mg \cdot kg^{-1}$ or neostigmine methylsulphate (●) 40 $\mu g \cdot kg^{-1}$ administered (↓) at 25% recovery of the control twitch height during anesthesia with nitrous oxide and either isoflurane (ISO/PIP), halothane (HALO/PIP), or droperidol/fentanyl (NLA/PIP) [Mean ± SEM].

Reversal of the residual neuromuscular blockade was easily accomplished within 10 minutes after the administration of neostigmine or edrophonium. However, depending on the anesthetic used, distinct clinical differences were observed between the effectiveness of the two reversal agents, as evidenced by the TOF percentages (Fig. 3). Mainly in patients treated with volatile anesthetics, the administration of edrophonium (0.5 $mg \cdot kg^{-1}$), in contrast to neostigmine, did not result in a TOF >70%, generally accepted as a threshold for sufficient recovery. A booster of half the initial dose, injected 10 minutes thereafter, resulted in only a marginal improvement in the TOF percentage.

Discussion

Our aim was to study pipecuronium under circumstances that mimic daily clinical practice as closely as possible. Therefore, we allowed only a small delay after induction of anesthesia to stabilize twitch height before injecting pipecuronium (average 10 minutes). The estimated doses of pipecuronium required for 95% depression of the twitch height (44.6, 46.9, and 48.7 $\mu g \cdot kg^{-1}$) during nitrous oxide and either isoflurane, halothane and droperidol/fentanyl anesthesia, respectively, did not differ. These doses are close to ED95 doses, ranging from 50 $\mu g \cdot kg^{-1}$ (7) to 59 $\mu g \cdot kg^{-1}$ (4). Similar ED95 doses have also been reported for pancuronium (8,9). We, therefore, consider these two compounds to be equipotent in blocking neuromuscular transmission.

With regard to the anesthetic technique used, no significant difference could be shown in the onset or magnitude of the neuromuscular blocking effects of pipecuronium between comparable doses when given in a single bolus injection.

Clinical duration of the total dose of 50 $\mu g \cdot kg^{-1}$ of pipecuronium was, however, dependent on the type of anesthetic employed. Both the overall comparisons and each of the possible pairwise comparisons were statistically significant, showing that the prolongation by the anesthetics of the neuromuscular effects of pipecuronium may be ranked as follows: isoflurane > halothane > droperidol/fentanyl.

The present study shows that pipecuronium is potentiated by inhalational anesthetics in a similar fashion as other nondepolarizing neuromuscular blocking agents. Ali and Savarese (10) demonstrated that d-tubocurarine requirements were reduced by half during 1.25 MAC of halothane and by approximately two-thirds during an equivalent concentration of isoflurane in comparison with the doses needed under "balanced nitrous oxide" anesthesia. Potentiation of d-tubocurarine, pancuronium, gallamine (11, 12), and vecuronium (13) has also been shown to be greater with isoflurane anesthesia than with halothane anesthesia. In the present study, the apparent lack of significant differences between the ED95 doses obtained under the various anesthetics (Table 1) can be explained by the relative brevity of the exposure time to the anesthetic before the administration of the muscle relaxant. This exposure time is even shorter than those in the above cited studies. After such a short period of time, alveolar concentrations of isoflurane and halothane would approximate only a part of the inspired concentrations (14), and tissue equilibrium would be even less. However, it should be realized that in the daily practice of anesthesia, the induction time is considerably shorter than in the present study; more importantly, muscle relaxants are usually given before the administration of the inhalational anesthetic. Consequently, at the start of anesthesia, no appreciable alteration of the effects of muscle relaxants can be expected. However, after some time, usually 30 to 40 minutes, the potentiating effects of the volatile anesthetics will be reflected by the prolonged clinical duration, prolonged duration of the maintenance doses, and longer recovery rates, as demonstrated in the present study. Therefore, the size of the maintenance doses or the time interval of earlier administration should depend on the expected duration of the operation and the type and concentration of the inhalational anesthetic used.

Residual neuromuscular block was readily antagonized in this study by both neostigmine and edrophonium. However, in contrast to neostigmine where the TOF recovery reached the ≥70% or higher level in all patients within 5 minutes of its administration, the same degree of reversal after edrophonium was reached only in patients treated with droperidol/fentanyl. The TOF recovery in patients receiving halothane or isoflurane was <70%, even 10 minutes after the administration of edrophonium. This necessitated the administration of the second dose (Fig. 3) of edrophonium, especially in patients receiving isoflurane for anesthesia. In most cases, this additional dose of edrophonium resulted in a minor but sufficient (>70%) increase in the TOF percentage. For these reasons, we consider edrophonium, at least in the doses used in this study (0.5 to 0.75 $mg \cdot kg^{-1}$), to be a less adequate and less safe antagonist of pipecuronium or probably of all long-acting muscle relaxants, than neostigmine, particularly in patients undergoing isoflurane anesthesia. The gradual increase in the TOF percentage after the second dose of edrophonium suggests minor beneficial effects of still higher doses of edrophonium.

Heart rate, blood pressure, and electrocardiogram were routinely monitored and registered during this study. No cardiovascular or other side effects that could be attributed to the administration of pipecuronium bromide were seen. These properties, if confirmed in widespread clinical use, will make pipecuronium the drug of choice for long operations, particularly in patients with cardiovascular disease.

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Hepatotoxicity and Metabolism of Isoflurane in Rats with Cirrhosis

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BADEN JM. Hepatotoxicity and metabolism of isoflurane in rats with cirrhosis. Anesth Analg 1989;68:214–18.

A rat model was used to determine whether isoflurane exacerbates liver dysfunction and whether its metabolism is changed in the presence of cirrhosis. Male Wistar rats were gavaged weekly with carbon tetrachloride until cirrhosis was well advanced. They and control rats without pretreatment with carbon tetrachloride and without cirrhosis were then exposed to 1.45% (1 MAC) isoflurane for 3 hours. Blood and urine samples were taken before, immediately, as well as 4, 24, 48, and 72 hours after anesthesia to measure liver function and isoflurane defluorination. After the last samples had been obtained, the rats were sacrificed and the liver removed for histologic examination and in vitro metabolic studies. Serum levels of SGOT and SGPT and inorganic fluoride production in rats with cirrhosis were similar to those in control rats without cirrhosis. Concentrations of cytochromes b_5 and p-450 and specific activities of microsomal defluorinase and several cytosolic enzymes were significantly lower in cirrhotic than in noncirrhotic liver, but their total amounts in whole liver were the same. The results imply that cirrhosis does not increase the risk of acute hepatotoxicity of isoflurane. They also demonstrate that metabolism of isoflurane and perhaps other volatile anesthetics may be unaffected in rats with cirrhosis, even though liver architecture is severely disrupted.

Key Words: ANESTHETICS, VOLATILE—isoflurane. TOXICITY, LIVER. LIVER, CIRRHOSIS.

Patients with cirrhosis of the liver may often require surgery to treat either complications of their liver disease or unrelated conditions. Controversy exists as to which anesthetics are safest for such patients. Many anesthesiologists believe that volatile anesthetics are safer than intravenous anesthetics because their elimination from the body does not depend to any extent on liver function. Others, however, believe that such anesthetics may exacerbate hepatic dysfunction either by altering liver blood flow or by producing toxic metabolites. If a volatile anesthetic is to be used, isoflurane would appear to be a particularly good choice because it is metabolized to only a small extent by the liver and is not known to produce hepatoxicity in patients with normal liver function. To test whether these favorable characteristics of isoflurane also apply in the presence of cirrhosis, we used an animal model established by Proctor and Chatamra (1,2) and used previously by us in a study with halothane (3). Our primary aim was to determine whether isoflurane administered to animals with moderate to severe cirrhosis exacerbates liver dysfunction. A secondary aim was to assess the metabolizing capability of cirrhotic liver for isoflurane and other substrates.

Methods

Institutional approval for the study was obtained from the Animal Care and Use Committee of Stanford University School of Medicine. Twenty-four male Wistar rats were individually ear-tagged and bedded on wood chips in plastic polycarbonate cages covered with stainless steel lids. They were allowed tap water and small animal chow at all times, except during anesthetic exposure when both were removed. After 2 weeks' quarantine, 0.05% sodium phenobarbital was added to the drinking water to produce enzyme induction. One week later, they were divided randomly into two groups each containing 12 rats. The first group (cirrhotic) was given carbon tetrachloride (CCl_4) to generate cirrhosis according to the method of Proctor and Chatamra (1,2). In brief, CCl_4 in corn oil (total volume 0.5 ml) was administered intragastrically once a week for 12

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weeks. The initial dose of CCl_4 for all animals was 0.04 ml, but thereafter, doses were individualized by basing the new dose on the degree of weight loss following the previous dose. By week 12, doses averaged 0.20 ml (range 0.12 to 0.28). After the last dose, phenobarbital was removed from the drinking water. The other group of rats (noncirrhotic) were handled similarly, but were gavaged with 0.5 ml of corn oil only.

Three weeks after the last dose of CCl_4, 1 ml of tail blood was taken for determination of background serum inorganic fluoride (F^-) and 1 week later, 2 ml of tail blood was taken for background serum chemistries (SMAC 20). Rats were then placed in individual metabolic cages and after a 3-day period to allow time for acclimitization and restoration of blood volume, a 24-hour urine collection was made. The next day, both groups were exposed for 3 hours to 1.45% [1 MAC in this species (4)] isoflurane in 50% oxygen. Exposure was performed in a 1000-liter Plexiglas chamber. Anesthetic concentration was monitored continuously with a Miran 1-F infrared gas analyzer and kept within 5% of the desired value. Oxygen concentration was monitored continuously with an IL-402 oxygen analyzer and maintained between 48 and 52%. The balance of gas in the chamber was nitrogen. Carbon dioxide concentration was intermittently monitored with a Beckman LB-2 analyzer and was kept <0.1%. Body temperature was measured continuously during anesthesia and maintained at 37 ± 1°C by means of a warming blanket.

At the end of anesthesia, 1 ml of tail blood was taken for determination of serum F^-, and rats were returned to their metabolic cages. At 4 and 24 hours after anesthesia, a further 1 ml of tail blood was taken for serum F^-, and at 48 hours, 2.5 ml of tail blood was taken for serum F^- and blood chemistries. Twenty-four hour urine collections were made for 3 days.

Seventy-two hours after anesthesia, 1 ml of blood was taken for a final determination of serum F^-, then each rat was killed by carbon dioxide overdose and the abdomen opened. The liver was immediately excised and weighed, and small samples were taken from each lobe for histologic examination. The remaining liver was weighed and perfused with ice cold 1.15% KCl and frozen in liquid nitrogen. Spleen, kidneys, and testes were excised, weighed, and fixed in 10% neutral buffered formalin. Histologic sections of all removed tissues were prepared and stained with hematoxylin and eosin. Liver sections were examined and graded for the degree of cirrhosis and superimposed acute hepatotoxic damage, according to previously established criteria (5,6). Other tissues were screened for acute and chronic toxic damage using standard histologic procedures. All histologic examinations were performed without knowledge of treatment.

Biochemical Methods

Frozen liver was thawed and homogenized with a Brinkmann polytron homogenizer in about three times its volume of 50-mM Sorenson buffer, pH 7.5. The homogenate was centrifuged in a Sorvall RC2-B centrifuge for 20 minutes at 17,400 *g*, 4°C. The supernatant was recentrifuged in a Beckman L2-65B ultracentrifuge for 60 minutes at 109,000 *g*, 4°C, and was used without further purification for glutathione transferase and acetylation assays. The microsomal pellet was resuspended in 50-mM Tris-HCl buffer, pH 7.4, and used for defluorination studies.

Protein concentrations for both fractions were determined by the Lowry method (7). Specific concentrations of microsomal cytochromes b_5 and p-450 were determined by spectrophotometric methods and calculated from extinction coefficients of 171 $mM^{-1}cm^{-1}$ (8) and 91 $mM^{-1}cm^{-1}$ (9), respectively.

Glutathione transferase activity was determined by the procedure of Habig et al. (10). In brief, a 3-ml reaction mixture contained: 5 mM glutathione (GSH); 1 mM 1,2-dichloro-4-nitobenzene (CDNB); and 0.1 M phosphate buffer. The conjugation of GSH and CDNB was measured with a Beckman Acta CIII spectrophotometer at 340 nm. Specific activity was expressed as μmol of conjugate formed per minute per milligram of cytosolic protein.

Acetylation rates of isoniazid (INH) and procainamide were measured according to the method of Kattner et al. (11), with some modification. A 3-ml reaction mixture contained: 2 mg cytosolic protein; 111.0 mM sodium pyrophosphate buffer, pH 9.0; 2 mM cosubstrate N,S-diacetyl-cysteamine (DAC); and 4 mM INH or 0.4 mM procainamide. Reaction was started by addition of DAC. Enzyme activity was determined with a Beckman Acta CIII spectrophotometer by measuring the change in absorbance at 303 nm for 10 minutes. Data were calculated as nmole acetyl-INH or acetyl-procainamide formed per milligram of cytosolic protein per minute.

Defluorination studies were performed as previously described by Rice and Talcott (12), with some modification. A-5 ml reaction mixture in a sealed tube contained: 5 mg microsomal protein; 50 mM Tris-HCl buffer, pH 7 4; NADPH regenerating system (200 mM glucose-6-phosphate, 20 mM $NADP^+$, and 0.6 units of G-6-P dehydrogenase); and approximately 1 mM isoflurane. Following a 10-minute incubation at 37°C,

Table 1. Body and Selected Organ Weights (g, mean ± SEM)

	Body	Liver	Spleen	Right Kidney	Left Kidney	Right Testes	Left Testes
Noncirrhotic (n = 12)	480 ± 11	17.3 ± 0.9	0.78 ± 0.04	1.74 ± 0.06	1.74 ± 0.05	1.96 ± 0.06	2.00 ± 0.04
Cirrhotic (n = 12)	451 ± 16	21.5 ± 0.9†	1.04 ± 0.06†	1.81 ± 0.06	1.80 ± 0.07	1.78 ± 0.05*	1.76 ± 0.06†

*Significantly different from noncirrhotic rats ($P < 0.05$).
†Significantly different from noncirrhotic rats ($P < 0.01$).

Table 2. Selected Serum Chemistries (mean ± SEM)

	A/G Ratio		SGOT*		SGPT*		Total Bilirubin†	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Noncirrhotic (n = 12)	1.1 ± 0.02	1.1 ± 0.04	101 ± 5.2	114 ± 10.1	71 ± 5.1	84 ± 4.3‡	0.04 ± 0.02	0.03 ± 0.02
Cirrhotic (n = 12)	0.9 ± 0.02§	0.9 ± 0.02§	93 ± 4.2	110 ± 9.3	84 ± 2.0§	101 ± 8.9‡§	0.39 ± 0.04§	0.36 ± 0.03§

*In IU/liter.
†In mg/dl.
‡Pre versus post values ($P < 0.01$).
§Significantly different from noncirrhotic rats ($P < 0.01$).

the reaction was terminated by submersing the incubation tube in boiling water. Levels of F^- were measured with an Orion ion-specific electrode and a Corning ion meter (13). Data were calculated as nmole F^- per milligram protein, or nmole cytochrome p-450, per minute. The F^- in blood and urine was measured directly with the ion-specific electrode.

Students paired or unpaired *t* tests with the Bonferroni correction for multiple comparisons were used to determine differences between the groups; $P < 0.05$ was considered statistically significant.

Results

All rats survived exposure to 1 MAC isoflurane for 3 hours and appeared to regain normal activity and health within several hours of anesthesia.

Body weights of CCl_4-treated rats were slightly less at death than those of untreated rats (Table 1). Weights of liver and spleen of CCl_4-treated rats were significantly higher and weights of testes were significantly lower than in untreated rats (Table 1). Ascites was present in all CCl_4-treated rats and was >10 ml in eight of these rats. These features are consistent with a diagnosis of cirrhosis of the liver with associated portal hypertension. The diagnosis was confirmed by histologic examination, which revealed moderate to severe degrees of cirrhosis in livers of all CCl_4-treated rats. However, there was no histologic evidence of acute hepatotoxicity in livers of either cirrhotic or noncirrhotic control rats. Sections from the testes of CCl_4-treated rats showed mild degrees of atrophy, whereas those from the spleen and kidneys were normal.

Albumin/globulin (A/G) ratio in CCl_4-treated rats was significantly decreased and total bilirubin significantly increased before anesthesia compared with values in untreated rats (Table 2). Values did not change significantly after anesthesia in either group. Levels of SGOT were not different before or after anesthesia either within or between groups (Table 2). In contrast, levels of SGPT in CCl_4-treated rats were slightly but significantly greater than in untreated rats both before and after anesthesia; they increased significantly after anesthesia to the same extent in both groups (Table 2).

There was no difference in serum F^- levels (Table 3) or urinary excretion of F^- (Table 4) between rats with or without cirrhosis over the 72-hour period after isoflurane anesthesia.

In vitro studies showed that concentrations of cytochromes b_5 and p-450 expressed per milligram of liver protein were significantly less in the cirrhotic livers than in livers of noncirrhotic rats (Table 5), but there was no difference in total amounts of these cytochromes in whole liver (Table 6). Microsomal defluorinase activity, a p-450-dependent reaction, was significantly less in cirrhotic than in noncirrhotic livers when expressed per milligram of liver protein, but was the same when expressed per nanogram of liver p-450 or per whole liver (Table 7). A similar pattern was seen for activities of the cytosolic enzymes, glutathione transferase, and N-acetyltrans-

Table 3. Serum Inorganic Fluoride Concentrations (μM, mean ± SEM)

	Preanesthesia	Postanesthesia (hours)				
		0	4	24	48	72
Noncirrhotic (n = 12)	1.6 ± 0.1	2.3 ± 0.1	5.3 ± 0.4	2.5 ± 0.3	1.9 ± 0.1	1.6 ± 0.1
Cirrhotic (n = 12)	1.4 ± 0.2	2.6 ± 0.2	6.0 ± 0.5	2.1 ± 0.3	1.6 ± 0.1	1.7 ± 0.1

Table 4. Urinary Inorganic Fluoride Excretion (nmole/24 hour, mean ± SEM)

	Preanesthesia	Postanesthesia		
		24	48	72
Noncirrhotic (n = 12)	31.3 ± 2.6	93.3 ± 7.2	49.3 ± 4.1	44.6 ± 1.9
Cirrhotic (n = 12)	29.2 ± 2.1	87.7 ± 9.8	42.3 ± 4.0	39.9 ± 4.2

Table 5. Metabolic Profile of Cirrhotic Liver* (mean ± SEM)

	Cytochrome b_5 (nmoles)	Cytochrome p-450 (nmoles)	Glutathione Transferase (μmoles/minute)	Isoniazid Acetylation (nmoles/minute)	Procainamine Acetylation (nmoles/minute)
Noncirrhotic (n = 12)	0.296 ± 0.018	0.292 ± 0.020	3.0 ± 0.15	7.29 ± 0.17	6.10 ± 0.21
Cirrhotic (n = 12)	0.243 ± 0.012†	0.226 ± 0.017†	2.2 ± 0.15‡	5.19 ± 0.30‡	3.53 ± 0.39‡

*Values are per miligram of protein.
†Significantly less than the noncirrhotic liver ($P < 0.05$).
‡Significantly less than the noncirrhotic liver ($P < 0.01$).

Table 6. Metabolic Capability of Total Liver (mean ± SEM)

	Cytochrome b_5 (μmoles)	Cytochrome p-450 (μmoles)	Glutathione Transferase (mmoles/minute)	Isoniazid Acetylation (μmoles/minute)	Procainamine Acetylation (μmoles/minute)
Noncirrhotic (n = 12)	1.00 ± 0.10	0.98 ± 0.08	10.1 ± 0.8	24.3 ± 1.9	20.5 ± 1.9
Cirrhotic (n = 12)	1.17 ± 0.17	1.06 ± 0.16	9.9 ± 1.0	24.2 ± 3.2	16.6 ± 3.0

ferase; they were reduced in cirrhotic compared with noncirrhotic liver when expressed per milligram of liver protein, but were about the same in whole cirrhotic and noncirrhotic livers (Tables 5 and 6).

Discussion

The animal model of cirrhosis in which rats are administered CCl_4 by oral gavage has been described previously in detail (1–3). Although the biochemistry and pathogenesis of CCl_4-induced cirrhosis in rats differs somewhat from alcoholic-induced cirrhosis in human patients, most of the clinical features are the same (14). In particular, both species can develop hepatic insufficiency and portal hypertension with ascites. As seen in the present study, the effects of isoflurane in rats with these clinical features are minimal; although there is a small increase in SGPT suggesting mild hepatotoxicity, it is not different from that seen in rats without cirrhosis. These findings are similar to those from an earlier study in which isoflurane was administered to rats with mild degrees of cirrhosis (15). They are different, however, from those seen in a recent study with halothane, in which liver dysfunction was exacerbated more in rats with moderate to severe cirrhosis than in rats without

Table 7. Isoflurane Defluorinase Activity (mean ± SEM)

	nmoles F^-/mg protein/minute	nmoles F^-/nmoles p-450/minute	μmoles F^-/liver/minute
Noncirrhotic (n = 12)	0.087 ± 0.01	0.306 ± 0.04	0.300 ± 0.03
Cirrhotic (n = 12)	0.066 ± 0.01*	0.321 ± 0.03	0.335 ± 0.03

*Significantly less than noncirrhotic rats ($P < 0.05$)

cirrhosis (3). Even so, halothane produced only minimal exacerbation of liver dysfunction, and it should not be too readily assumed that isoflurane is a more favorable anesthetic in such animals, especially because halothane and isoflurane were not directly compared in the same study.

The present study found that total in vivo metabolism of isoflurane, as assessed by serum F^- levels and urinary F^- excretion, was unchanged in rats with cirrhosis. A similar finding was seen with halothane (3). It is not immediately apparent why this should be the case, especially because disruption of liver architecture in rats with moderate to severe cirrhosis is so marked on histologic examination. To investigate the possible reasons, we studied the content of cytochromes in cirrhotic liver and the metabolic capability of cirrhotic liver for various substrates. Concentrations of cytochromes b_5 and p-450, which are important constituents of the mixed function oxidase system responsible for the metabolism of all volatile anesthetics, were reduced in cirrhotic compared with normal livers. Other investigators have measured concentrations of cytochrome p-450 in livers of patients with alcoholic cirrhosis (16) and rats with CCl_4-induced cirrhosis (17–19) and have found similar reductions. However, when the total liver content of these cytochromes was determined, there was no difference between cirrhotic and normal livers. Apparently, the enlargement of the liver during the development of cirrhosis compensated for the reduced concentrations. A similar pattern was observed with the p-450-dependent defluorinase, glutathione transferase, and the acetylators of isoniazid and procainamide; activity per milligram of protein (or gram of liver) was reduced in cirrhotic livers, but total activity in whole livers was the same as that in normal livers. The reduced concentration of cytochromes and enzymes in the cirrhotic liver is not unexpected given the reduced density of hepatocytes seen on histologic examination. Moreover, the normal content of cytochromes and enzymes in the whole cirrhotic liver provides a ready explanation for why total in vivo metabolism of isoflurane and halothane is unchanged if there is concurrent hepatomegaly.

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Effects of Halothane and Enflurane on Conduction Velocity and Maximum Rate of Rise of Action Potential Upstroke in Guinea Pig Papillary Muscles

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OZAKI S, NAKAYA H, GOTOH Y, AZUMA M, KEMMOTSU O, KANNO M. Effects of halothane and enflurane on conduction velocity and maximum rate of rise of action potential upstroke in guinea pig papillary muscles. Anesth Analg 1989;68:219–25.

Using standard microelectrode techniques, the effects of halothane and enflurane on the maximum rate of rise of action potential upstroke ($\dot{V}max$) and conduction velocity of excitation were compared with those of fast sodium channel blockers in isolated guinea pig papillary muscles. Lidocaine and tetrodotoxin decreased the square of the conduction velocity in proportion to the decrease in $\dot{V}max$. In contrast, halothane and enflurane only slightly affected $\dot{V}max$, but decreased the conduction velocity in a concentration-dependent manner. These results suggest that these volatile anesthetics affect conduction velocity by a mechanism different from that of fast sodium channel blockers. Caution should be used when these anesthetics are administered to patients receiving class 1 antiarrhythmic agents or who have pre-existing intraventricular conduction disease.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane. HEART—CONDUCTION VELOCITY, ACTION POTENTIAL.

It is well known that volatile anesthetics affect not only cardiac pump function, but also the cardiac conduction system (1). In vivo and in vitro studies have shown that halothane and enflurane depress automaticity of the sinoatrial node and conduction velocity in the atrioventricular node (2–8). Because the action potentials of these cardiac tissues depend largely on Ca^{++} influx through slow channels, the inhibitory effects of these anesthetics are suggested to be caused by their slow channel blocking action (1). Indeed, it has been reported that halothane depresses slow action potentials in partially depolarized papillary muscles (9) and decreases the Ca^{++} current in isolated cardiac cells (10). However, the effects of volatile anesthetics on cardiac sodium channels and conduction velocity in fast response fibers, such as Purkinje fibers and ventricular muscles, have not been well established. Recently, we reported that high concentrations of halothane and enflurane decrease the conduction velocity in atrial and ventricular tissues in which rapid sodium current is a factor governing the propagation of excitation (8). Based on a one-dimensional cable theory, several models describing action potential propagation have been constructed (11,12), and the following relation has been derived from experimental observations and mathematical simulations:

$$\theta^2 \propto \frac{a\ \dot{V}max}{Cm\ Ri\ Vp}$$

where θ is conduction velocity, a is fiber radius, $\dot{V}max$ is the maximum rate of rise of action potential upstroke, Cm is membrane capacitance per unit area, Ri is the axial resistivity and Vp the height of the action potential. From this equation, it can be predicted that a decrease in conduction velocity is usually accompanied by a decrease in $\dot{V}max$ unless internal longitudinal resistance and/or membrane capacitance are altered. In fact, Buchanan et al. (13) have demonstrated that in guinea pig papillary muscles, fast sodium channel blockers produced a decrease in $\dot{V}max$, which was proportional to the decrease in the

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square of conduction velocity. However, in terms of the effects of halothane on $\dot{V}$max of fast response fibers, reported results have been conflicting. Hauswirth (14) reported that halothane at a concentration of 2% significantly depressed $\dot{V}$max in sheep Purkinje fiber. In contrast, Gallagher et al. (15) demonstrated that in canine Purkinje fibers, halothane in concentrations of 0.5 to 2.0% did not affect $\dot{V}$max. Lynch et al. (9) also reported that halothane in concentrations of 0.5 to 3.0% did not significantly change $\dot{V}$max in guinea pig papillary muscles. Therefore, the present study was undertaken to determine whether halothane and enflurane can affect $\dot{V}$max and conduction velocity of excitation in guinea pig papillary muscles. We examined the effects of these anesthetics on the relation between $\dot{V}$max and conduction velocity, and compared them with the effects of the fast sodium channel blockers tetrodotoxin and lidocaine. By doing so, we hoped that we would gain greater insights into the mechanisms by which volatile anesthetics affect the cardiac conduction system.

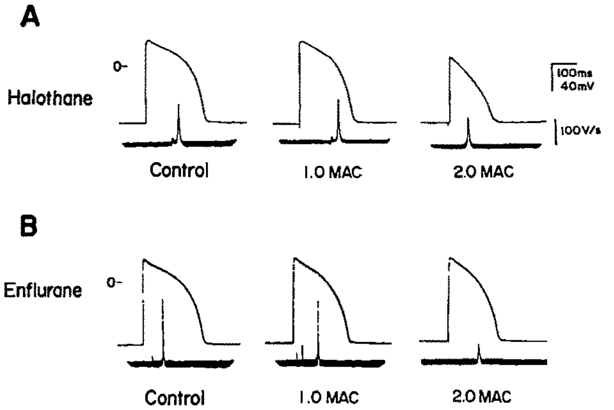

Figure 1. Effects of halothane (A) and enflurane (B) on the action potential and $\dot{V}$max in guinea-pig papillary muscles driven at 1.0 Hz. In panel A, control action potential (left), action potential recorded 20 min after 1.0 MAC (middle) and 2.0 MAC halothane (right) are shown. In panel B control action potential (left), action potential recorded 20 min after 1.0 MAC (middle) and 2.0 MAC enflurane (right) are depicted. The upper and lower tracings in each record indicate the transmembrane potential and dV/dt (on expanded time base). Calibrations in panel A are applicable to panel B.

Methods

This study was approved by the Animal Research Committee of Hokkaido University School of Medicine. Guinea pigs of either sex, weighing 250 to 400 g, were stunned with a blow on the head and the hearts were quickly removed. To remove the intracavity blood, the hearts were immersed in an oxygenated Tyrode solution at room temperature, which had the same composition as superfusion solution. Papillary muscles having a diameter <1 mm were dissected from the right ventricle of the hearts under a microscope. Such a slim preparation was expected to be well-oxygenated under superfusion and stable conduction over a long experimental period. The preparations were transferred to a tissue bath of 5-ml volume and superfused at a rate of 10 ml/minute with a modified Tyrode solution containing the following composition (in mM): NaCl, 125; KCl, 4; $NaHCO_3$, 25; NaH_2PO_4, 1.8; $MgCl_2$, 0.5; $CaCl_2$, 2.7; and glucose, 5.5. The solution was gassed with 95% O_2 + 5% CO_2, and the temperature was kept constant at 33.0 ± 1.0°C.

The preparations were stimulated at a rate of 1.0 Hz using a bipolar, enamel-coated, stainless steel electrode at the cut end. Stimuli were rectangular pulses of 1-ms duration at twice the diastolic threshold, delivered from an electronic stimulator (Nihon Kohden, SEN 6100) through an isolation unit (Nihon Kohden, SS-302J). Two separate microelectrode impalements were made in a line along the long-axis of the preparation. Transmembrane potentials were recorded from both microelectrodes in each preparation using glass microelectrodes filled with 3M KCl (resistance of 10 to 30 MΩ). The microelectrodes were coupled via an Ag/AgCl junction to a high impedance amplifier (W-P Instruments, FD 223) equipped with an input capacity neutralization unit (W-P Instruments, FC-23). An agar bridge containing 3M KCl was used as a common reference electrode. Electronic differentiators with a linear output from 50 to 1000 V/second were used for measuring the maximum rate of rise of action potentials. These amplified signals were displayed on an oscilloscope (Nihon Kohden, VC-9), photographed on 35-mm film, and recorded on a chart recorder (Watanabe Sokki, WR 3101).

Conduction time was defined as the time between the peaks of the differentiated upstroke signals. Using a stereomicroscope with a calibrated ocular grid (Olympus SZ), the interelectrode distance was measured with accuracy in a range of ±0.05 mm, and the conduction velocity was calculated by dividing interelectrode distance by the conduction time.

After an equilibration period of 120 minutes, control recordings were made and the preparations were exposed to a solution containing the lowest concentrations of volatile anesthetics or drugs. The concentration was increased stepwise at an interval of 20 minutes, and recordings of action potentials were repeated. The concentrations of halothane and enflurane tested in the present study were 0.5, 1.0, 1.5, and 2.0 maximum allowable concentration (MAC). Halothane (Takeda, Osaka, Japan) and enflurane (Abott, Chicago, Illinois) were introduced into the

Table 1. Effects of Halothane on Action Potential Parameters of Guinea Pig Papillary Muscles

	RMP (−mV)	APA (mV)	APD_{20} (ms)	APD_{50} (ms)	APD_{90} (ms)	$\dot{V}$max (V/second)	CV (m/second)
Control	90.3 ± 0.8	128.7 ± 2.0	140.0 ± 8.8	220.8 ± 8.1	253.3 ± 7.5	211.7 ± 25.7	0.37 ± 0.04
0.5 MAC	92.7 ± 1.8	128.0 ± 1.6	137.5 ± 9.4	218.3 ± 8.9	250.8 ± 8.9	201.7 ± 27.0	0.34 ± 0.04
1.0 MAC	93.0 ± 1.8	126.7 ± 1.2*	126.3 ± 8.2*	201.7 ± 9.3*	235.8 ± 9.5*	202.5 ± 24.9	0.31 ± 0.05
1.5 MAC	90.7 ± 0.9	123.3 ± 2.1*	105.5 ± 12.0*	184.2 ± 12.5*	213.5 ± 11.3*	210.8 ± 31.9	0.21 ± 0.06*
2.0 MAC	88.7 ± 1.3	117.0 ± 3.9*	95.8 ± 10.0*	164.2 ± 12.8*	200.8 ± 11.4*	189.2 ± 29.9*	0.09 ± 0.02*

*$P < 0.05$ from the control value by paired t test. Values are expressed as mean ± SEM of six preparations.

Abbreviations: APA, action potential amplitude; APD_{20}, action potential duration 20% repolarization; APD_{50}, action potential duration at 50% repolarization; APD_{90}, action potential duration 90% repolarization; CV, conduction velocity; RMP, resting membrane potential; $\dot{V}$max, maximum rate of rise of action potential upstroke.

Table 2. Effects of Enflurane on Action Potential Parameters of Guinea Pig Papillary Muscles

	RMP (−mV)	APA (mV)	APD_{20} (ms)	APD_{50} (ms)	APD_{90} (ms)	$\dot{V}$max (V/second)	CV (m/second)
Control	92.8 ± 1.7	131.2 ± 0.9	132.0 ± 6.0	211.0 ± 5.3	245.0 ± 4.8	258.0 ± 31.0	0.47 ± 0.05
0.5 MAC	92.0 ± 1.7	130.8 ± 0.7	126.0 ± 8.4	205.0 ± 5.8	241.0 ± 5.1	258.0 ± 30.0	0.46 ± 0.05
1.0 MAC	90.8 ± 0.9	127.4 ± 1.2	101.0 ± 9.6*	176.0 ± 10.0*	211.0 ± 10.0*	253.0 ± 26.4	0.40 ± 0.04
1.5 MAC	91.6 ± 2.0	116.0 ± 2.4*	87.0 ± 9.0*	154.0 ± 9.6*	189.0 ± 10.7*	245.0 ± 28.8	0.18 ± 0.03*
2.0 MAC	91.6 ± 2.0	116.0 ± 2.4*	71.0 ± 5.5*	125.0 ± 6.3*	160.0 ± 7.8*	245.0 ± 30.7	0.07 ± 0.01*

*$P < 0.05$ from the control value by paired t test. Values are expressed as mean ± SEM of 5 preparations.

Abbreviation as in Table 1.

oxygen-carbon dioxide mixture through appropriate vaporizers: Fluotec Mark 3 (Cyprane Keighley) and Enflurane Vaporizer E3 (Kimura), respectively. The vaporizer settings used to administer 1 MAC of halothane and enflurane were 0.74 and 1.68%, respectively. The actual concentrations of these volatile anesthetics in the bath medium were determined by gas chromatography (Shimadsu, GC-4A PTF). Lidocaine (Sigma Chemical) was dissolved in the distilled water containing equimolar HCl as a stock solution (10 mM), which was used to prepare the superfusion solution containing various concentrations (10, 30, 60, 100, and 300 μM) of lidocaine. Tetrodotoxin (Sankyo) was dissolved in distilled water as a stock solution (1 mg/ml), which was used to prepare the superfusion solution containing 0.5 to 16 μM of tetrodotoxin. Only results of experiments in which both impalements were maintained throughout are presented here, and the others were discarded.

All data are presented mean ± standard error. Statistical analyses of changes of action potential parameters and conduction velocity were performed using paired Students t test. Statistical significance was established when the probability value was <0.05. The correlation coefficients and regression equations were calculated by least squares analysis.

Results

The actual concentrations, determined by gas chromatography, of halothane and enflurane in the superfusate were as follows: halothane, 5.4 ± 0.4 mg/dl at the 1.0 MAC setting, 10.0 ± 0.7 mg/dl at 2.0 MAC; enflurane, 10.3 ± 0.3 mg/dl at the 1.0 MAC setting, 20.3 ± 0.4 mg/dl at 2.0 MAC. The concentration of enflurane was higher than that of halothane when the same MAC levels were compared.

Figure 1 shows typical changes in action potentials during the exposure to halothane and enflurane. These action potentials were obtained from the proximal recording site, close to the bipolar stimulation electrode. Both anesthetics produced concentration-dependent decreases in action potential amplitude (APA) and action potential duration (APD) without affecting resting membrane potential (RMP). The data obtained from six preparations exposed to halothane and five preparations exposed to enflurane are summarized in Tables 1 and 2, respectively. Again, APA and APD were decreased in a concentration-dependent manner. However, the maximum rate of rise of action potential upstroke ($\dot{V}$max) was only slightly affected by enflurane at the concentrations used in the present study. Halothane at 1.0 MAC did not significantly decrease $\dot{V}$max. Increasing the concentration of halothane to the 2.0 MAC produced a slight but significant decrease in $\dot{V}$max (Table 1). The conduction velocity was significantly decreased by these volatile anesthetics in concentrations >1.5 MAC (Tables 1 and 2).

We examined effects of tetrodotoxin and lidocaine, fast sodium channel blockers, on the relations between conduction velocity and $\dot{V}$max in one and four

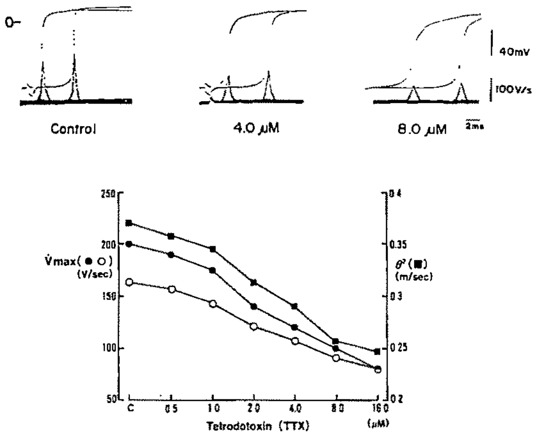

Figure 2. Effects of tetrodotoxin (TTX) on interelectrode conduction velocity and V̇max in a guinea-pig papillary muscle. In upper panels, upstroke of two action potentials (upper traces) and dV/dt (lower traces) recorded before (control) and after 4.0 and 8.0 μM tetrodotoxin are shown on the same time scale. Changes of V̇max of two action potentials (open and closed circles) and interelectrode conduction velocity (θ, closed squares) in this experiment are depicted in lower panel. V̇max and θ are on the ordinate, and concentrations of TTX are on the abscissa. C indicates control values.

preparations, respectively. Representative examples of changes in V̇max and conduction velocity produced by tetrodotoxin and lidocaine are depicted in Figures 2 and 3. After various concentrations of tetrodotoxin and lidocaine, the decrease in conduction velocity was in parallel with the decrease in V̇max. Either tetrodotoxin or lidocaine decreased V̇max values of two action potentials and increased the conduction time between two recording sites in a concentration-dependent manner. V̇max and conduction velocity were normalized to the respective values obtained under control conditions, and V̇max and the square of conduction velocity are plotted on the ordinate and the abscissa, respectively, in Figure 4. The solid lines represent the relation that would be obtained if the decrease in V̇max was proportional to the decrease in the square of conduction velocity. Figure 4 also shows that lidocaine and tetrodotoxin induce changes in V̇max proportional to the changes in the square of the conduction velocity. Lidocaine-induced changes in action potentials, obtained from proximal recording sites, and conduction velocity values in four preparations are summarized in Table 3. Lidocaine at a concentration of 10 μM did not produce any significant changes in action potential parameters in the preparations stimulated at 1.0 Hz. Lidocaine in concentrations >60 μM significantly decreased conduction velocity, concomitantly with a significant decrease in V̇max.

In contrast to fast sodium channel blockers, halothane and enflurane decreased conduction velocity without a proportional decrease in V̇max. As shown in Figures 5 and 6, halothane and enflurane in concentrations >1.5 MAC markedly decreased conduction velocity; although V̇max was slightly decreased or unchanged by these anesthetics. Figure 7 shows

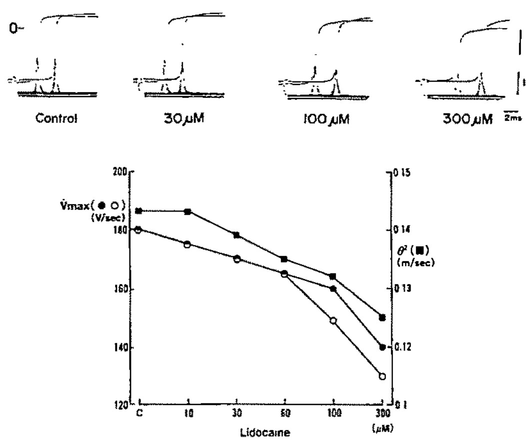

Figure 3. Effects of lidocaine on interelectrode conduction velocity and V̇max in a guinea-pig papillary muscle. Upstroke of two action potentials and dV/dt before (control) and after 30, 100 and 300 μM lidocaine are demonstrated in upper panels. In lower panel changes of V̇max of two action potentials (open and closed circles) and interelectrode conduction velocity (closed squares) are shown.

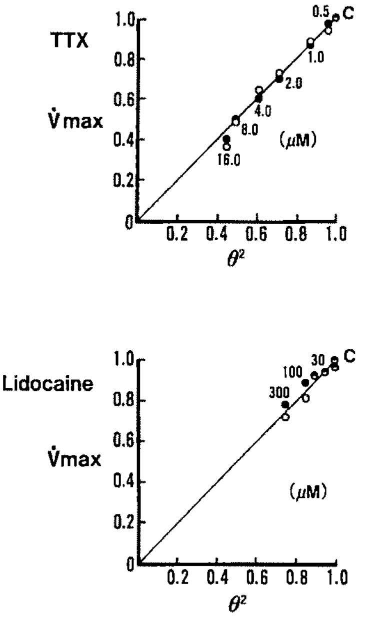

Figure 4. Effects of tetrodotoxin (TTX) and lidocaine on V̇max and conduction velocity. Upper and lower panels show plots of the data from the experiments presented in Figures 2 and 3, respectively. In these panels, the data are normalized to control conditions, and V̇max (ordinate) is plotted against the square of conduction velocity (abscissa). Open and closed circles indicate V̇max values of two action potentials recorded from different cells. Drug concentration (μM) are indicated in the figure. Linear regression analyses gave the slope of 1.07 and 0.85 for the TTX and lidocaine experiments, and the correlation coefficients were 0.99 and 0.96, respectively. Thus, the results are well fit by the relationship that V̇max is proportional to the square of conduction velocity.

Table 3. Effects of Lidocaine on Action Potential Parameters of Guinea Pig Papillary Muscles

	RMP (−mV)	APA (mV)	APD_{20} (ms)	APD_{50} (ms)	APD_{90} (ms)	V̇max (V/second)	CV (m/second)
Control	95.5 ± 2.8	130.0 ± 1.1	152.5 ± 11.9	226.2 ± 16.5	256.2 ± 18.6	168.7 ± 18.0	0.34 ± 0.07
10 μM	92.5 ± 0.5	128.5 ± 1.5	146.2 ± 11.9	217.5 ± 17.6	250.0 ± 19.6	166.2 ± 17.3	0.34 ± 0.07
30 μM	93.0 ± 0.5	128.5 ± 1.5	145.0 ± 10.9	213.7 ± 15.4*	246.2 ± 17.6*	162.5 ± 16.1	0.34 ± 0.07
60 μM	93.5 ± 0.9	128.1 ± 1.1*	137.5 ± 12.6	203.7 ± 15.7*	238.7 ± 17.1*	157.5 ± 16.1*	0.32 ± 0.06*
100 μM	94.0 ± 1.4	124.5 ± 2.2*	126.2 ± 10.2*	195.0 ± 11.7*	230.0 ± 16.7*	138.7 ± 11.9*	0.30 ± 0.06*
300 μM	94.0 ± 1.4	109.7 ± 8.4*	107.5 ± 7.2*	175.0 ± 14.8*	216.2 ± 16.2*	121.2 ± 10.8*	0.27 ± 0.05*

*$P < 0.05$ from the control value by paired *t* test. Values are expressed as mean ± SEM of four preparations.
Abbreviations as in Table 1.

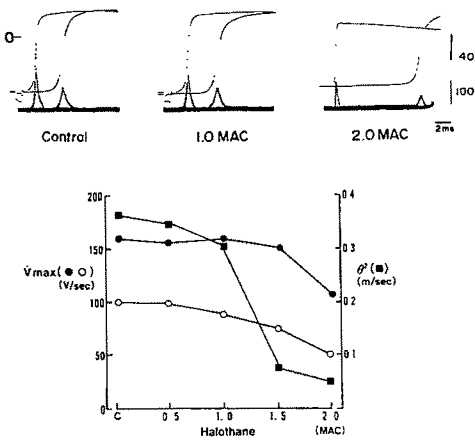

Figure 5. Effects of halothane on interelectrode conduction velocity and V̇max in a guinea-pig papillary muscles. Upstroke of two action potentials and dV/dt before (control) and after 1.0 and 2.0 MAC halothane are shown in upper panels. Changes of V̇max (open and closed circles) and interelectrode conduction velocity (θ, closed squares) in this experiment are depicted in lower panel. V̇max and θ are on the ordinate, and the concentrations of halothane are on the abscissa. C indicates control.

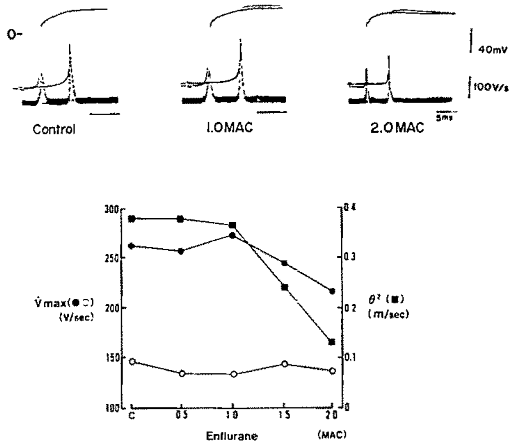

Figure 6. Effects of enflurane on interelectrode conduction velocity and V̇max in a guinea-pig papillary muscle. Upstroke of two action potentials and dV/dt before (control) and after 1.0 and 2.0 MAC halothane are shown in upper panels. Note that the time scale of the right panel (2.0 MAC) is different from the other two panels. Changes of V̇max (open and closed circles) and interelectrode conduction velocity (θ, closed squares) are depicted in the lower panel. V̇max and θ are on the ordinate, and concentrations of halothane are on the abscissa. C indicates control.

the effects of various concentrations of halothane and enflurane on V̇max and conduction velocity at a constant stimulation frequency of 1.0 Hz. The changes in V̇max and conduction velocity produced by these volatile anesthetics did not fit the proportional relation between the decrease in V̇max and that in the square of the conduction velocity. In other words, halothane and enflurane slowed conduction without decreasing V̇max.

The relation between changes in V̇max and decreases in the square of the conduction velocity, which were obtained from all preparations exposed to lidocaine ($n = 4$), halothane ($n = 6$), and enflurane ($n = 5$), are demonstrated in Figure 8. Lidocaine produced decreases in V̇max that were proportional to the decreases in the square of the conduction velocity. The slopes, obtained by least square analyses, were 0.83 ± 0.01 in four preparations and close to the theoretical value of 1.0. However, in all the preparations exposed to halothane and enflurane, conduction velocity was decreased disproportionally to the change in V̇max (Fig. 8). Least square analyses gave the slopes of 0.11 ± 0.06 for halothane and −0.03 ± 0.06 for enflurane, which were very far from the theoretical value of 1.0. Although there were no significant differences between the slope values for halothane and enflurane, these values were significantly different from the slope values for lidocaine ($P < 0.001$).

In certain experiments, we washed out the anesthetics and fast sodium channel blockers for 20 minutes after the completion of experiments, and confirmed that action potential changes and slowed conduction reverted toward the control values.

Discussion

Recently, we demonstrated that in isolated rabbit hearts, high concentrations of halothane and enflurane slow not only atrioventricular conduction, but

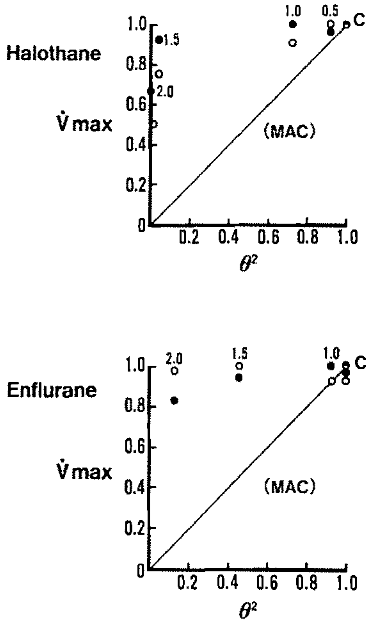

Figure 7. Effects of halothane and enflurane on $\dot{V}$max and conduction velocity. Upper and lower panels show plots of the data from the experiments presented in Figures 5 and 6, respectively. In these panels, the data are normalized to control condition, and $\dot{V}$max (ordinate) is plotted against the square of conduction velocity (abscissa). Open and closed circles indicate $\dot{V}$max values of two action potentials recorded from different cells. Concentrations of these volatile anesthetics are shown in this figure (MAC). Linear regression analyses gave the slopes of 0.31 and 0.07 for the halothane and enflurane experiments, respectively.

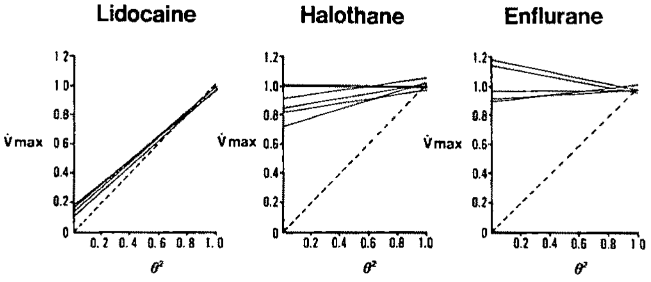

Figure 8. Relationships between changes in $\dot{V}$max (ordinate) and decreases in the square of the conduction velocity (abscissa) in preparations exposed to lidocaine (left panel, $n = 4$), halothane (middle panel, $n = 6$) and enflurane (right panel, $n = 5$). In each experiment linear regression analysis gave a straight line (sloping solid line), and all data, including representative examples shown in Figures 4 and 7, are demonstrated. Dotted lines represent the relationship which would be obtained if the decrease in $\dot{V}$max were proportional to the decrease in the square of the conduction velocity (i.e. slope value = 1).

also intraatrial and intraventricular conduction in which the rapid sodium inward current plays an important role (8). However, reports concerning the effects of halothane on $\dot{V}$max of the fast action potentials have been contradictory (9,14,15). Therefore, the present study was undertaken to determine the effects of volatile anesthetics on $\dot{V}$max and conduction velocity in fast response fibers. The results presented here indicate that halothane and enflurane decrease conduction velocity with little influence on $\dot{V}$max in guinea pig papillary muscles.

We utilized guinea pig papillary muscles because it has been reported that the suitably selected preparations demonstrate one-dimensional propagation of excitation (16). The one-dimensional cable theory predicts that $\dot{V}$max, an indirect estimate of the fast sodium current, should be approximately proportional to the square of conduction velocity (11–13). Indeed, in the present study, pharmacologic blockade of fast sodium channels by tetrodotoxin and lidocaine produced decreases in $\dot{V}$max that were proportional to the decreases in the square of the conduction velocity. These findings are in agreement with the results reported by Buchanan et al. (13). In contrast to the fast sodium channel blockers, halothane and enflurane slowed conduction, but produced little change in $\dot{V}$max. These findings suggest that volatile anesthetics may decrease conduction velocity by mechanism other than fast sodium channel blockade. One possibility is that these volatile anesthetics might alter the cable properties of guinea pig papillary muscles. When the internal longitudinal resistance and/or the membrane capacitance are increased, a decrease in conduction velocity is expected to occur (11,12,17). In this context, it has been reported that halothane produces a marked increase in internal resistance and a decrease in input capacitance in sheep Purkinje fibers (18). A marked increase in internal resistance can lead to a decrease in conduction velocity, although the reduced capacitance can counterbalance the effect to some extent. The present study shows that enflurane and halothane behave similarly in terms of the relation between $\dot{V}$max and the square of conduction velocity. Thus, not only halothane, but also enflurane, might increase the longitudinal resistance, resulting in the decrease in conduction velocity, as observed in the present study.

However, we cannot exclude the possibility that volatile anesthetics might inhibit the fast sodium current and thereby decrease conduction velocity. In the present study, $\dot{V}$max was slightly inhibited by a high concentration (2.0 MAC) of halothane. It has been reported that halothane reduces the sodium current not only in nerve tissue (19,20), but also in cardiac tissue (21). Theoretically, electrical uncoupling between cells can increase $\dot{V}$max, and thereby might mask the decrease in $\dot{V}$max resulting from the direct inhibitory effect on the fast sodium current. Therefore, the fast sodium channel blocking action of these volatile anesthetics might play a role in the slowed conduction. Whatever the mechanism involved, the present results show that these volatile anesthetics decrease conduction velocity with little change in V̇max.

Recently Gallagher et al. (15) demonstrated that electrophysiologic effects of quinidine on action potential and conduction velocity in canine Purkinje fibers were much more pronounced in the presence of halothane. The present study suggests that enflurane as well as halothane may interact adversely with the fast sodium channel blockers, slowing conduction in the fast response cardiac tissues, such as Purkinje fibers, atrial, and ventricular muscles. Therefore, these volatile anesthetics should be administered with caution to the patients receiving fast channel blocking agents (for example, lidocaine and quinidine). In addition, halothane and enflurane may potentially impair conduction, especially in patients with pre-existing intraventricular conduction disease such as bundle branch block.

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Status of the Match in Anesthesiology: 1988

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FAUST RJ, ROSE SH, WEDEL DJ, MILDE LN. Status of the match in anesthesiology: 1988. Anesth Analg 1989;68:226–8.

The majority of anesthesia program directors agreed 2 years ago to use the National Resident Matching Program (NRMP) as the mechanism for appointing senior medical students to second postgraduate year positions in anesthesiology. Eighty-seven applicants for the Mayo Clinic program were surveyed to measure the level of cooperation with the NRMP by programs and applicants. Low percentages of applicants reported pressures to sign contracts (22.4%) or make verbal commitments before February (32.8%). The frequency of these incidents was extremely low when considered in light of the number of applicant interviews reported by the applicants who responded. Nonparticipation in the match is a more important problem than infractions of NRMP rules.

Key Words: EDUCATION, RESIDENCY PROGRAMS.

Concern has been voiced regarding compliance with rules governing the National Resident Matching Program (NRMP) in anesthesiology. Although second-year positions in anesthesiology have been offered for the past 2 years through the NRMP Advanced Program for Students, some question the justice of this system. There are no data in the literature to indicate the level of compliance with NRMP rules or applicant satisfaction with the anesthesia match. This study was designed to investigate these areas.

Methods

A survey was undertaken to assess the perceptions of applicants to the Mayo Clinic residency in anesthesiology regarding the NRMP and the delay of the dean's letter submission until November 1, a change implemented in the fall of 1987. Questionnaires were mailed to all 87 medical school seniors who completed applications to the program in anesthesiology in 1987. Surveys were anonymous except for the designation M, P, or U, signifying whether the applicant 1) matched into the Mayo Clinic program (matched group); 2) was passed over before the Mayo Clinic program filled (passed group); or 3) was unmatched because of being low on the Mayo rank order list or excluded from that list (unmatched group). Because the designation of the groups was arbitrary with respect to the rank order list, no statistical comparison was performed on intergroup differences.

Results

Table 1 describes applicant data and response rates for the survey. The overall response rate was 66.7%; 100% of the subgroup who matched with Mayo responded. Although two applicants applied to only four programs, the number of programs applied to included one person who reported having applied to 83 programs in anesthesiology. The average applicant interviewed at 9.4 programs; 537 applicant interviews were reported by the 58 responding applicants. Sixty-six percent of applicants matched into their first-ranked program, and 21% of applicants matched into their second choice.

Table 2 gives data collected from the questionnaire items, which attempt to measure how widespread noncompliance on the match actually was. Overall, 22% of respondents answered that one or more programs had pressured them to sign a contract—clearly against NRMP rules. Only two applicants reported this pressure from more than one program; therefore, 15 incidents were reported following 537 applicant interviews. Pressure to make a verbal com-

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Table 1. Applicant Data

	Matched	Passed	Unmatched	All Responses
Response Rate:	14/14 (100%)	18/22 (82%)	26/51 (51%)	58/87 (66.7%)
1. To how many anesthesiology training programs did you apply?				
(Mean)	11.7	18.8	17.9	16.9
2. With how many anesthesiology training programs did you interview?				
(Mean)	7.8	11.4	8.9	9.4

Table 2. NRMP Cooperation

	Matched	Passed	Unmatched	All Responses
3. How many programs pressured you to sign a contract before February? (% of applicants answering 1 or more)	7.1%	22.2%	30.8%	22.4%
4. How many programs pressured you for a verbal commitment before February? (% of applicants answering 1 or more)	0.0%	33.3%	50.0%	32.8%
5. How many programs encouraged you by saying that you would definitely match with them if you ranked them first? (% of applicants answering 1 or more)	71.4%	61.1%	69.2%	67.2%

Table 3. Applicant Support for the NRMP and Delayed Dean's Letter Mailing

	Matched	Passed	Unmatched	All Responses
6. Should the G-1 match in anesthesiology be continued in future years? ____Yes ____No				
(Yes)	100.0%	100.0%	92.0%	96.5%
7. Should the G-2 match in anesthesiology be continued in future years? ____Yes ____No				
(Yes)	92.9%	83.3%	92.3%	89.7%
8. The dates of dean's letter mailings and rank order list submission were delayed in 1987–1988 to give applicants more time to apply. Do you view this as a change for the better ____, worse ____, or neutral ____.				
(Overall)	Better (55.2%)	Worse (22.4%)	Neutral (22.4%)	

mitment before February was reported as having happened 37 times to 19 (32.8%) of the 58 responding applicants. Question 5 measured the frequency of verbal mechanisms for encouraging, however indirectly, high ranking of a program. This reflects a widespread practice commonly used as a recruiting technique.

Table 3 gives results for two questions that measure the applicants' overall support for the match in anesthesiology. Widespread support for the NRMP was demonstrated by applicants, contradicting the opinion sometimes expressed that applicants in anesthesiology do not favor the NRMP and would prefer direct appointment. Question 8 generated a mixed response in reference to the delay in dean's letter mailing until November 1, implemented for the first time in 1987.

Discussion

This study failed to demonstrate that program directors are pressuring applicants to sign contracts or make early verbal commitments as proscribed by NRMP rules. Although some might construe a program director's encouraging an applicant that he or she would definitely match into that program if the applicant ranked the program first (question 5) to be a violation of NRMP rules, it is not. NRMP policy does not condemn this practice but states: "Any indication concerning how a residency program director regards an applicant or how an applicant regards a program which may be made prior to the submission of the Rank Order List is not binding" (1).

Incomplete surveys can bias results, but it was believed that if infractions of the NRMP rules are common, applicants affected by this problem would be more likely to respond, falsely elevating the incidence of cheating reported by the survey. Although slightly higher fractions of the respondents in the passed and unmatched groups indicated contract or verbal commitment pressure from programs, these infractions were reported by a minority of those responding.

The study demonstrated a low frequency of NRMP infractions, in contrast to the claims of some program directors. Low percentages of applicants reported pressures to sign contracts (22.4%) or make verbal commitments before the match date (32.8%). Because the 58 applicants responding to the survey had interviewed at 537 programs, the number of infractions per applicant program interview was extremely low. Only 2.8% of applicant interviews were followed by pressure to sign a contract before the match date. Only 6.9% of applicant interviews were followed by pressure to make a verbal commitment before the match date.

Another part of the survey studied factors motivating program selection by applicants. Those responding indicated whether factors were very important, moderately important, or unimportant when they ranked programs. "Guaranteed availability of a position" was clearly the lowest ranked factor in all three groups. If many candidates chose programs in response to pressures either to sign contracts or to make verbal commitments, more would have ranked this factor as important. Instead, resident morale, program didactic content, and case complexity were the most important factors cited by the applicants for making their decisions.

Nonparticipation in the match is a more important problem than infractions of the NRMP rules. In 1988, 109 of 165 anesthesia residency programs participated (Table 4). The majority of nonparticipating programs were non-university based programs offering relatively fewer positions than the average program that participated. It is difficult to obtain data on how many positions are being held outside the match for medical graduates. NRMP policy is that positions filled by physicians already in other training programs or practice "need not be listed with the NRMP" (2). Offering such a position to a senior medical student clearly violates the intent of the NRMP.

Nearly equal numbers of NRMP applicants matched into anesthesiology positions in 1987 and 1988; the lower percentage of programs filling might be due to the large increase in PG-2 positions offered in 1988 (Table 4). It is difficult to determine the number of medical school seniors who signed into nonparticipating programs.

Table 4. NRMP Positions in Anesthesiology (3,4)

	1987	1988
Programs participating	104	109
PG-1 applicants matched	262	235
PG-1 positions offered	323	270
% offered positions filled	81.1	87.0
PG-2 applicants matched	461	486
PG-2 positions offered	642	723
% offered positions filled	71.8	67.2
PG-1 and PG-2 applicants matched	723	721
PG-1 and PG-2 positions offered	965	993
% offered positions filled	74.9	72.6

Eighty-seven percent of those responding to the survey matched into their first- or second-ranked program. Although anesthesiology is a competitive field, this study suggests that opportunities are good enough for most applicants to match into a program of their choosing. Candidates should not feel insecure about turning down a contract in the fall if they wish to train in a participating program that they believe is superior.

Comments were also solicited in our survey, giving candidates another opportunity to anonymously document NRMP infractions. Only one person referred to this problem, and this comment should be considered by all program directors: "I feel that the match should be obligatory for all anesthesia residency training programs. The present situation of some programs participating while others are not creates an environment for shady dealings." Although we could not document a high incidence of NRMP infractions, we share the belief that full participation by all programs would be beneficial to both applicants and residency programs.

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A Randomized Comparison Between Midazolam and Thiopental for Elective Cesarean Section Anesthesia

I. Mothers

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CRAWFORD ME, CARL P, BACH V, RAVLO O, MIKKELSEN BO, WERNER M. A randomized comparison between midazolam and thiopental for elective cesarean section anesthesia. I. Mothers Anesth Analg 1989;68:229–33

In a randomized blind trial midazolam (0.3 mg kg^{-1}) was compared with thiopental (4 mg kg^{-1}), both combined with meperidine-nitrous oxide, for elective cesarean section anesthesia in 40 women. We found no statistically significant differences between thiopental and midazolam at induction, during operation or recovery with regard to maintenance doses, change in maternal neurologic status based on a modified Glasgow Coma Scale, systolic blood pressure, and heart rate. Induction time was 120 seconds with midazolam and 111 seconds with thiopental. There were significant differences with regard to diastolic blood pressure. Side effects occurred with approximately equal frequencies, but vomiting was significantly more frequent after thiopental. Perivenous tenderness and erythema occurred in four patients, all after thiopental. Midazolam appears to be a suitable alternative to thiopental for the induction and maintenance of anesthesia for elective cesarean section.

Key Words: ANESTHESIA, obstetric. ANESTHETICS, INTRAVENOUS—thiopental, midazolam. HYPNOTICS, BENZODIAZEPINES—midazolam.

In cesarean section anaesthesia, one important concern is the possible transfer of anesthetic agents across the placenta. Other drugs applied for this purpose, thiopental, ketamine, and diazepam, possess high degrees of lipid solubility and rapid maternal-fetal equilibration (1–9).

The limited metabolic capacity of neonates, the long biological half-life of diazepam, the possible deleterious hemodynamic effects of thiopental, the psychotomimetic side effects of ketamine, and the possibility of preoperative awareness are some of the inducements that stimulate research on new short acting induction agents with amnesic properties. Midazolam is a short acting water soluble imidazobenzodiazepine. Many studies have established its suitability for induction of anesthesia (10–12), its favorable side effect profile (13), and its ability to provide anterograde amnesia (14).

The aim of the present investigation was to compare midazolam with thiopental for induction of anesthesia in patients scheduled for elective cesarean section focusing on maternal efficacy and safety.

Methods and Patients

Forty women of mixed parity, physical status ASA 1 or 2, at term, aged 18 to 40 years, and scheduled for elective cesarean section were allocated randomly to receive either midazolam or thiopental for induction of general anesthesia.

Patients were blind as to treatment, doctors/nurses administering treatment procedures were unaware as to outcome/evaluation, whereas doctors/nurses evaluating results were blind as to treatment. The trial was conducted in accordance with the Helsinki II Declaration and approved by the local Ethics Committee. Informed consent was obtained from each patient.

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Exclusion criteria included untreated hypertension (>150/90 mm Hg), preeclampsia or eclampsia, antepartum hemorrhage, signs of fetal distress (amniotic fluid meconium staining, fetal heart rate >160 or <120 beats/minute) multiple pregnancy, diabetes mellitus, cardiac-, renal-, or hepatic disease, any medication on the day of surgery prior to induction of anesthesia, and dependence on drugs or alcohol. No premedication was given.

Prior to induction of anesthesia, all patients were tilted toward the left lateral position. Preoxygenation was performed for at least 3 minutes and after injection of tubocurarine 3 mg intravenous and atropine 0.6 mg intravenous, anesthesia was induced with midazolam 0.3 mg kg^{-1} intravenous over 30 seconds or with thiopental 4 mg kg^{-1} intravenous. Tracheal intubation was facilitated by a bolus of succinylcholine 1.5 mg kg^{-1} intravenous. Until division of the umbilical cord, anesthesia was maintained with nitrous oxide 67% in oxygen with an infusion of succinylcholine chloride (0.2% solution) for relaxation.

Levels of neuromuscular blockade were monitored utilizing a peripheral nerve stimulator (Biometer).

After division of the umbilical cord, meperidine 0.75 mg kg^{-1} intravenous was given the patients in both groups, with supplementary doses of 0.25 mg kg intravenous injected whenever one or more of the following were observed: movement, phonation, presence of lid reflex, 25% increase of arterial blood pressure above the preanesthetic baseline levels, cardiac dysrrhythmias, lacrimation, sweating, swallowing, coughing, bronchospasm, or 25% increase of heart rate over the preanesthetic value.

Observation for efficacy

Time for induction of anesthesia (time between completion of intravenous injection and until loss of ciliary reflex), duration of anesthesia, induction doses, amounts of meperidine and succinylcholine used, signs of insufficient anesthetic depth (as listed previously), perioperative awareness, (defined either as movement between the time of administration of succinylcholine and intubation, or expressed by the patient at a 24 hour interview), and postoperative recovery as assessed by means of a modified Glasgow Coma Scale (15). This scale was considered appropriate as it is one of the few scales for estimating the general functional condition of the cerebrum, that is equivalent to direct assessment of the degree of sedation by means of determining the level of consciousness on basis of eye reactions, verbal and other motor reactions. Estimation of the latter function was modified to minimize various degrees of influence on the brain stem. Minimum and maximum of the scale are 0–10 points, respectively.

Table 1. Demographic Data and Anesthetic Time Intervals

	Midazolam	Thiopental
Age (yr)	29.5 (19–40)	28.3 (19–40)
Weight (kg)	67.0* (54–94)	77.8 (54–111)
Weeks of pregnancy	39.9 (38–44)	39.9 (34–44)
Induction (sec)	120 (60–240)	111 (40–300)
Time until umbilical cord was clamped (min)	7.5 (4–12)	6.5 (4–14)
Duration of anesthesia (min)	70 (55–80)	70 (55–80)
Blood loss (ml)	400 (200–1000)	400 (200–1500)

Details of patients, induction time, time until umbilical cord was clamped, duration of anesthesia and blood loss. Median (range); *$P < 0.05$.

Blood loss, heart rate, and arterial blood pressure were recorded. All changes of vital signs were stratified for the purpose of analysis. Furthermore, pain on injection of the induction agent, postoperative erythema, or tenderness (24, 72 hour) at the site of injection were noted, as well as any adverse reactions.

Statistical evaluation

Statistical methods were Mann-Whitney Rank Sum test and Fisher test for between group comparisons. Differences in scores on Glasgow Coma Scale, arterial blood pressure, heart rate, and respiratory rate were evaluated by a non-parametric model (16) corresponding to analysis of variance for a two factor design with repeated measures on one factor. A probability of <0.05 was considered as significant.

Results

Apart from the difference between body weights ($P < 0.05$), there were no significant differences between the two groups with regard to demographic data, induction time, time until umbilical cord was clamped, duration of anesthesia, and blood loss (Table 1).

Table 2 shows medications during anesthesia. It was only necessary to inject one dose of midazolam or thiopental for induction of anesthesia. The median

Table 2. Medication

	Midazolam	Thiopental
Induction agent	0.31	4.9
(total mg; kg^{-1})	(0.30 -0.45)	(3.2–9.0)
Succinyl chloride	7.8	7.5
(total mg kg^{-1})	(3.9–15.9)	(1.7–18.6)
Meperidine (mg kg^{-1})	1.6*	1.4
	(1.2–3.0)	(0.6–1.9)

Median (range); *P < 0.05.

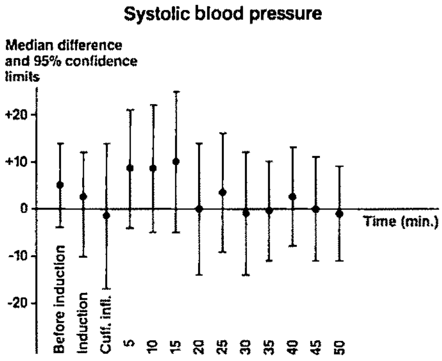

Figure 1. Differences in median systolic blood pressures, expressed as midazolam data, minus thiopental data, with 95% confidence limits.

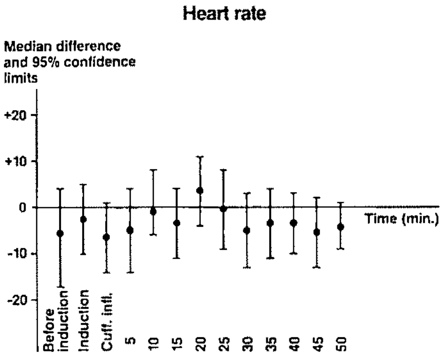

Figure 2. Differences in median heart rates, expressed as midazolam data, minus thiopental data, with 95% difference limits.

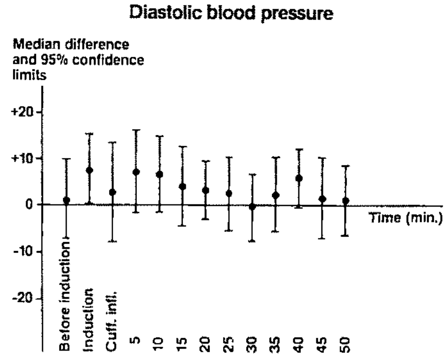

Figure 3. Differences in median diastolic blood pressures, expressed as midazolam data, minus thiopental data, with 95% confidence limits.

Table 3. Modified Glasgow Coma Scale Score During Recovery—Maximum Possible Score: 10 Points

	Midazolam	Thiopental	Median Difference
After 30 min	9.0	8.9	+0.1
	(5–10)	(6–10)	(−0.7 and +0.9)
After 60 min	9.8	9.8	0.0
	(8–10)	(8–10)	(−0.3 and +0.3)
After 120 min	9.9	9.9	0.0
	(8–10)	(9–10)	(−0.2 and +0.2)

Median (95% interpercentile range) and median difference (95% confidence limits)

doses were 21.8 mg for midazolam and 400 mg for thiopental. Supplementary doses of the induction agent were administered to two patients in the midazolam group and one patient in the thiopental group. The median amount of meperidine needed was significantly greater in the midazolam group (1.6 mg kg^{-1}) than that in the thiopental group (1.4 mg kg^{-1}).

Heart rate and systolic blood pressure varied significantly with time in both groups (v.s.), but the changes were similar in the two groups (Fig. 1 and 2). The diastolic blood pressure also varied significantly with time in both groups (v.s.), but the median difference between the midazolam and the thiopental groups was statistically significant during induction, 7.9 mm Hg groups, but not after induction (Fig. 3).

The modified Glasgow Coma Scale scores for awareness during recovery were without statistically significant differences between groups, but increased with time within both groups (Table 3).

At 24 hour, three cases of perivenous tenderness and one case of erythema were discovered, all in the thiopental group. The difference between groups was not statistically significant. Perivenous tenderness persisted in one case for 14 days.

The frequency of side effects appears in Figure 4. Nausea and dizziness were the most common postoperative side effects, whereas vomiting occurred only in the thiopental group ($P < 0.05$). "Others," refer to incisional pain, headache, sedation, fatique, crying, and visual difficulties. The total number of patients with side effects in the midazolam and the thiopental groups averaged 65% and 60%, respectively, on the day of operation as compared with 10% and 15%, respectively, the day after surgery. No cases of peroperative awareness were reported.

Discussion

Previous studies almost unanimously found midazolam induction to be slower than thiopental induction,

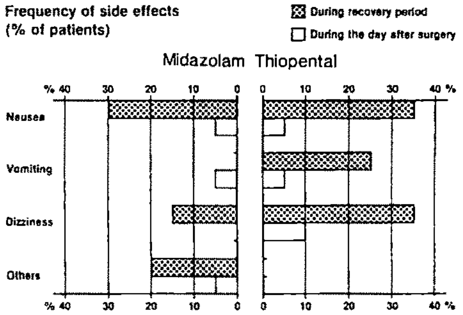

Figure 4. Side effects during recovery and the first postoperative day.

a difference greater in unpremedicated patients (17–19).

With outpatients having termination of pregnancy, we confirmed significant differences in induction time as well as times to postanesthetic awareness between midazolam and thiopental (12). In the present study, however, we were not able to detect any statistical differences regarding induction intervals, maintenance dosages of induction agents, or postanesthetic recovery.

When focusing on the absolute values, the recorded median induction intervals were longer (120 seconds with midazolam and 111 seconds with thiopental) in both groups than in the outpatient study (40 seconds versus 61 seconds, respectively) although median induction doses were greater in the present study (21.8/400 mg versus 14.8/350 mg). Dose-response relationships of midazolam (20) revealed that, after 0.3 mg kg^{-1} injected intravenous over 20 seconds in 166 patients, the time from end of injection until "asleep" was between 60 and 119 seconds in 31% of patients and from 40 to 59 seconds with 16%. The older the patients the shorter the induction time. Reves et al. (21) and Dundee et al. (22) relate longer induction times to high serum albumin concentrations. We believe that our induction times were increased due to greater volume of distribution (V_D) and plasma clearance in pregnant women and/or different experimental conditions, e.g., unpremedicated patients.

Increase in the metabolic capacity of the liver of pregnant women is suspected to affect clearance and elimination half-life values (23). On the other hand (24–26), all report that midazolam kinetics in pregnant women undergoing cesarean section are similar to those in healthy subjects, though Greenblatt et al. (27) demonstrated higher volumes of distribution (V_D) in women and with obesity.

Total amounts of induction agents used in the two groups proved to be low when considering the fairly long duration of anesthesia (70 minutes).

Perioperative meperidine requirements were greater in the midazolam group, where the median weight of the women was approximately 10 kg lower than that in the thiopental group.

The only signs of differences in anesthetic depth were minor differences of circulatory parameters. Group comparisons revealed differences of diastolic blood pressures on induction and variation of the other values (heart rate and systolic pressure) with time, presumably documentation of the desired low degree of anesthesia with this type of patient, though we stress that perioperative awareness was absent in all cases. Premedication might have abolished the minor cardiovascular responses. Indeed, Lebowitz et al. (28) demonstrated that midazolam tended to produce less pronounced changes in heart rate and mean arterial blood pressure than thiopental in premedicated patients.

In accordance with previous studies (10,29), we observed no cases of venous complications with midazolam.

Vomiting was significantly more frequent in the thiopental group (0 versus 5), a difference not observed in a previous study (12).

We conclude that midazolam is a suitable alternative to thiopental for induction and maintenance of anesthesia for elective cesarean section.

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A Randomized Comparison Between Midazolam and Thiopental for Elective Cesarean Section Anesthesia: II. Neonates

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In a randomized blind trial, the general condition of 40 neonates was assessed following midazolam- or thiopental-based general anesthesia for elective cesarean section. Among 19 neonatal neurobehavioral observations and tests, statistically significant differences between the midazolam and the thiopental groups were rare. However, a statistically significant interaction with regard to body temperature, general body tone, and arm recoil was observed where results were inferior for midazolam, although only within the first 2 hours.

It was concluded that midazolam is as safe as thiopental for the induction and maintenance of elective cesarean section anesthesia in neonates.

Key Words: ANESTHESIA, OBSTETRICAL. ANESTHETICS, INTRAVENOUS—midazolam, thiopental. HYPNOTICS, BENZODIAZEPINES—midazolam.

The condition of the neonate following cesarean section may be influenced substantially by the anesthetic technique. The uteroplacental blood flow and oxygenation, as well as placental transfer of the anesthetic, are the main influencing factors. High lipid solubility favors rapid induction of anesthesia, but unfortunately also favors placental transfer of the induction agent.

The suitability of midazolam, a short-acting water-soluble imidazobenzodiazepine, for the induction of anesthesia in nonpregnant patients has been established (1–3). Placental transfer of midazolam given as premedicant prior to elective cesarean section has been investigated with the conclusion that "the kinetic data support the use of midazolam in obstetrics" (4). Having compared the effects of midazolam and diazepam in pregnant ewes, Conklin et al. (5) suggested that midazolam might be useful for sedation during labor and delivery and for induction of general anesthesia for cesarean section.

Consequently, the aim of this study was to compare the effect of midazolam and thiopental on the general condition of the neonate following cesarean section anesthesia with these induction agents.

Patients and Methods

The study group comprised 40 healthy women at term and scheduled for elective cesarean section (6). The present material deals with the resulting 40 neonates. The trial was conducted in accordance with the Helsinki II Declaration and approved by the Local Ethics Committee. Informed consent was obtained from the mother of each neonate.

Exclusion criteria for the neonates were any injury at birth, congenital abnormality, gestational age (7) as assessed by clinical examination of <37 weeks or >42 weeks, birth weight <2.5 kg or >4.6 kg, placental infarctions, retroplacental hematoma, abnormal umbilical cord, signs of respiratory distress syndrome, and development of systemic infection.

Prior to induction of anesthesia, all patients were tilted toward the left lateral position. Preoxygenation was performed for at least 3 minutes, and following injection of tubocurarine (3 mg intravenously [IV]) and atropine (0.6 mg IV), anesthesia was induced with midazolam (0.3 mg kg^{-1} IV over 30 seconds or with thiopental (4 mg kg^{-1} IV over 30 seconds).

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Tracheal intubation was facilitated by a bolus of succinylcholine (1.5 mg kg^{-1} IV). Until division of the umbilical cord, anesthesia was maintained with nitrous oxide (67%) in oxygen, with an infusion of succinylcholine choride (0.2% solution) for relaxation.

The times for delivery, clamping of umbilical cord, and first cry were recorded. Apgar scores were determined 1 and 5 minutes after delivery (8). Resuscitative procedures such as intermittent positive pressure ventilation (IPPV) by face mask, tracheal intubation, external cardiac massage, and administration of sodium bicarbonate were recorded if performed. The following events were recorded if present during hospitalization: convulsions, tetany, coma, hypoglycemia, respiratory depression, cardiac arrest, or jaundice, as well as any adverse reactions as assessed by clinical or laboratory evaluations.

The following 19 neonatal neurobehavioral tests (9) and examinations were performed 1, 2, 3, 4, 6, 8, 12, and 24 hours after delivery and once daily during hospitalization by one of the authors: response to sound and light, rooting reflexes, sucking reflex, palmar grasp, resistance against pull (to sitting position), arm recoil, startle reaction, general body tone, alertness, muscle tremors, consolability when crying, irritability, rapidity of response to stimulation, degree of spontaneous activity, self-quieting activity, hand to mouth facility, degree of excitement when stimulated, feeding pattern, and body temperature. Apart from response to light and sound (binominal rating scale), the neonatal neurobehavioral scores were all measured by a 4-point ordinal scale (0 = no reaction, 1 = minimal reaction, 2 = moderate reaction, 3 = severe reaction).

Because the principal design was bifactorial as to treatment and time, with repeated measurements on the latter, a nonparametric model of combined Mann-Whitney and Friedmann tests corresponding to a two-way analysis of variance was employed. Results are expressed as median differences with 95% confidence limits. Variations are indicated by median values and dispersion by range only.

Comparability between groups was assessed by χ^2 test and Mann-Whitney Rank U tests. P values <0.05 were considered statistically significant.

Results

One neonate in the midazolam group who developed respiratory distress syndrome and systemic infection, and one neonate in the thiopental group with congenital heart disease and failure, were excluded from the study. Demographic data (Table 1) revealed no significant differences between the two groups regarding sex, birth weight, and gestational age ($P > 0.10$ in each case). The median Apgar scores (Table 2) 1 and 5 minutes after delivery in the midazolam group was 9.3 (range 5 to 10) and 9.9 (range 7 to 10), respectively, were not significantly different from the median scores of 9.6 (range 5 to 10) and 9.9 (range 8 to 10), respectively, in the thiopental group. The median time differences between delivery, clamping of umbilical cord, and first cry revealed no differences between the groups ($P > 0.10$ in each case). Examination of maternal placenta revealed no cases of infarction, hematoma, or abnormal umbilical cord. Resuscitation procedures were limited to IPPV by face mask in five neonates in the midazolam group and in three in the thiopental group ($P > 0.10$).

Table 1. Details of Neonates (median and [range])

	Midazolam	Thiopental
Sex	9M, 10F	7M, 12F
Birth weight (g)	3405 (2950–4400)	3590 (2500–4550)
Gestational age (score)	7.6 (6–10)	8.0 (6–10)

Gestational age (7) score 0 to 14. Score < 6 N gestational age < 37 weeks. Score ≥ 11 N gestational age > 42 weeks.
Abbreviations: F, female; M, male.

Table 2. Apgar Rating After Delivery (median and [range])

	Midazolam	Thiopental
1 Minute	9.3 (5–10)	9.6 (5–10)
5 Minutes	9.9 (7–10)	9.9 (8–10)

Adverse reactions, both clinical and physiologic, were limited to one neonate with respiratory depression on the first day and one neonate with hypoglycemia and one with jaundice on the third day (all in the midazolam group). Response to sound and light revealed no differences between the groups. Among the 19 neonatal neurobehavioral observations and tests (Fig. 1), statistically significant differences between the midazolam and the thiopental groups were infrequent. However, a statistically significant difference was observed with regard to body temperature, general body tone, and arm recoil. Results were inferior with midazolam, although only within the first 2 hours after delivery. Comparable but insignificant variations occurred with regard to palmar grasp, resistance against pull, and startle reaction.

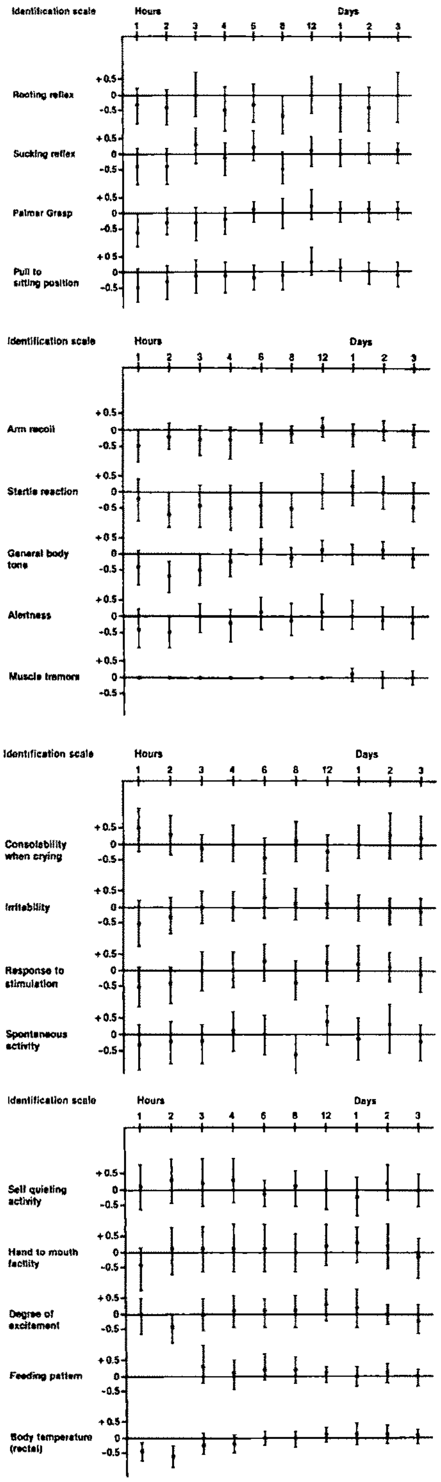

Figure 1. The neonatal neurobehavioral examinations and tests for each examination time are expressed as median differences—midazolam minus thiopental—with 95% confidence limits.

Discussion

Neonatal neurobehavioral tests were introduced as "a valuable way to assess the effects of maternally administered drugs on the newborn, effects of a more subtle nature than can be measured by Apgar scoring alone" (9). It was stated that they represented a simple, rapid, and reproducible technique of assessing some aspects of newborn behavior in the early hours of life.

Floppy infant syndrome after maternal diazepam and/or nitrazepam administration was first described in 1977 (10). The syndrome was not clearly defined, but was described as: "primary or secondary apnoea, hypotonia, poor sucking, risk of aspiration of feeds, hypothermia, unresponsive, colour changes, sleepy and passive." Warnings have been issued against the use of high maternal doses of diazepam, flunitrazepam, lorazepam, nitrazepam, or oxaxepam in view of the possible occurrence of floppy infant syndrome (11).

The present material revealed differences between thiopental and midazolam only with regard to body temperature, arm recoil, and general body tone. No group differences indicated floppy infant syndrome.

There were no differences among the mothers that might explain the differences found among the children (6). Though the pharmacokinetic studies (12) revealed substantial variations in plasma levels of the drugs in question between neonates, no correlation was found between plasma levels and results of the neurobehavioral tests. The only clinical manifestation of possible drug influence during this period was respiratory depression in one neonate in the midazolam group.

Midazolam when used as a sedative-anxiolytic agent 30 minutes before elective cesarean section was not associated with deleterious effects on the newborn children (4). Two previously published reports studied diazepam and thiopental as induction agents of anesthesia for cesarean section (13,14). By focusing on Apgar scores and acid-base status, no differences were found between groups. Midazolam is considered to be transferred through the placenta more slowly than diazepam, oxazepam, or lorazepam (11).

The present findings support the suggestion that midazolam is as safe as thiopental for induction and maintenance of anesthesia for elective cesarean section.

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A Randomized Comparison Between Midazolam and Thiopental for Elective Cesarean Section Anesthesia:
III. Placental Transfer and Elimination in Neonates

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BACH V. CARL P, RAVLO O, CRAWFORD ME, JENSEN AG, MIKKELSEN BO, CREVOISIER C, HEIZMANN P, FATTINGER K. A randomized comparison between midazolam and thiopental for elective cesarean section anesthesia: III. Placental transfer and elimination in neonates. Anesth Analg 1989;68:238–47.

Forty neonates delivered by cesarean section were studied, half being delivered of mothers in whom anesthesia was induced with midazolam (0.3 mg/kg intravenously) and half of mothers given thiopental (4 mg/kg). At delivery, blood samples from mother and the umbilical vein were drawn for determination of plasma concentrations of thiopental, midazolam, and α-hydroxymidazolam. Over the next 60 hours, three blood samples were drawn using a randomized procedure of two blood samples at 30 different times. Placental transfer, expressed as the umbilical/maternal concentration ratio, was 0.96, 0.66, and 0.28, respectively, for thiopental, midazolam, and α-hydroxymidazolam. The transfer of thiopental was significantly more rapid than the transfer of midazolam and α-hydroxymidazolam. The population average of elimination half-life in neonates was 6.3 hours for midazolam and 14.7 hours for thiopental. Both values are substantially larger than those found in previous studies in adults.

Key Words: ANESTHESIA, OBSTETRIC. ANESTHETICS, INTRAVENOUS—thiopental, midazolam. HYPNOTICS, BENZODIAZEPINES—midazolam. PHARMACOKINETICS, THIOPENTAL, MIDAZOLAM.

This report describes some neonatal pharmacokinetic parameters of midazolam and thiopental, especially data on placental transfer and elimination, as part of a larger study comparing the use of midazolam and thiopental in cesarean section (1,2). Knowledge of neonatal pharmacokinetics, especially elimination of intravenous anesthetics, is scanty. Prolonged elimination is, however, expected since hepatic metabolic capacity is not fully developed (3).

Thiopental is often the drug of choice for induction in patients having cesarean section under general anesthesia, despite the rapid placental transfer of thiopental and other highly lipid-soluble agents (4–10). The relatively new benzodiazepine, midazolam, is water-soluble (in its salt form) when injected intravenously, but at physiologic pH, the structure changes and midazolam becomes lipid-soluble (11). In adults, the elimination half-life of midazolam is about 3 hours, one of the shortest among the benzodiazepines (12,13).

Material and Methods

The data from the 40 neonates reported here represent part of the data obtained in the same 40 neonates that are reported elsewhere (1,2). The trial was conducted in accordance with the Helsinki II Declaration and approved by the Local Ethics Committee. Informed consent was obtained from each mother at the preanesthetic examination.

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The anesthetic management (1) consisted basically of the random induction of anesthesia with midazolam, 0.3 mg/kg intravenously (IV), in half of the ASA physical status I mothers having elective cesarean section and with thiopental, 4 mg/kg IV, in the other half. Muscle relaxation was obtained by succinylcholine. Until delivery, the mothers were ventilated with nitrous oxide (67%) in oxygen. No other drugs were given, and anesthesia was not supplemented during this period.

As soon as the umbilical cord was clamped and transsected, blood samples were drawn from the cubital vein contralateral to that used for induction of anesthesia in the mothers and from the umbilical vein for determination of the concentrations of midazolam, its main metabolite α-hydroxymidazolam, and thiopental. Over the next 60 hours, three similar samples of capillary blood were drawn from each neonate in accordance with a randomized procedure of two blood samples at 30 different times. This was done to minimize the number of blood samples drawn from each neonate. The samples were drawn 15, 30, 45, and 60 minutes after delivery. Thereafter, samples were drawn with increasing intervals throughout the sampling period.

Immediately after sampling, plasma was separated and frozen for future analysis. The concentrations of thiopental were determined using high pressure liquid chromatography (14). The concentrations of midazolam and α-hydroxymidazolam were determined by gas chromatography with electron capture detection (15,16). The limit of detection was 0.2 mg/l for thiopental. For midazolam and α-hydroxymidazolam, the limit of detection was 2 μg/l in maternal and umbilical blood and 5 μg/l in neonatal capillary blood.

Results are presented as median values with interquartile range in brackets, if not otherwise stated. Statistical analysis consisted of nonparametric Mann-Whitney *U* test of two groups and Spearman's rank correlation test.

To estimate the pharmacokinetic parameters that describe the plasma concentration time profile in the neonates, the computer package of NONMEM was used (17). This method was preferred to "classical" pharmacokinetic analysis because only a few samples were available for each individual. The NONMEM program yields estimates of the population mean of the pharmacokinetic parameters and their interindividual variance. Since the "dose" (the amount of drug in the body at the time of delivery) received by the neonates is not known, the basic pharmacokinetic parameters, clearance and volume of distribution, cannot be determined and only elimination rate constants can be estimated.

The decrease in midazolam plasma concentration with time could be described by a monoexponetial decay. Therefore, the following pharmacostatistical model was used in the NONMEM analysis:

$$\mathrm{In}\ C_{ij} = \mathrm{Const} + \eta 1j - (k \cdot e^{\eta 2j}) \cdot t_{ij} + \varepsilon_{ij} \tag{1}$$

where the subscripts i and j refer to one i^{th} measurement in the j^{th} neonate, k is the population mean of the elimination rate constant of midazolam, t is the time of measurement, $\eta 1$ and $\eta 2$ are random errors describing the variability of the pharmacokinetic parameters among the neonates, and ε is the residual (intraindividual) variability of the plasma concentration measurements. Equation 1 assumes that all neonates received the same dose, and describes the differences in the unknown amount of drug in the body at the time of delivery by random variability. NONMEM estimates the fixed effects, Const and k and the variances of $\eta 1$, $\eta 2$, and ε.

The analysis of the thiopental data revealed that the concentration time profile was better described by a biexponential decay:

$$C(t) = C1^{-\lambda 1t} + C2 \cdot e^{-\lambda 2t} \tag{2}$$

where C(t) is the plasma concentration at the specific time t. All other parameters are hybrid constants, that is, complex functions. C1 and C2 are coefficients of the concentration and represent the intercept on y-axis for each exponential segment of the curve, λ1 is the distribution rate constant, and λ2 is the elimination rate constant.

Results

Maternal hemodynamic data are presented in detail elsewhere (1). In summary, there was a small change in blood pressure and heart rate with time. However, no single time interval was associated with a significant change. There was no difference between thiopental and midazolam. During anesthesia, no side effects were seen in mothers.

The general condition of the neonates was good, as described elsewhere (2). Apgar ratings after 1 and 5 minutes were 9.3 (range 5 to 10) and 9.9 (range 7 to 10) in the midazolam group and 9.6 (range 5 to 10) and 9.9 (range 8 to 10) in the thiopental group. In a total of 19 neurobehavioral tests, a small but significant interaction between the two groups was seen within the first 2 hours in body temperature, general body tone, and arm recoil.

Table 1. Placental Transfer

	No.	Mother	Umbilical	Umb/Mother
Thiopental (mg/liter)	20	4.31 (3.12–6.50)	4.65 (3.25–5.69)	0.96 (0.79–1.15)
Midazolam (μg/liter)	20	339 (234–617)	318 (188–411)	0.66 (0.50–1.05)
α-Hydroxymidazolam (μg/liter)	20	22.0 (11.8–50.8)	5.0 (3.0–9.1)	0.28 (0.12–0.48)

Venous plasma concentrations of drugs and the metabolite of midazolam in umbilical vein and neonatal/maternal concentration ratios (Umb/Mother). Results are medians, with interquartile ranges in brackets.

Table 2. Elimination

		Midazolam	Thiopental
Population mean			
	λ_1	*	1.68 (0.88)
	λ_2	0.11 (0.010)	0.047 (0.007)
Interindividual variability			
	λ_1	*	†
	λ_2	38%‡ (10)	†
Residual error‡		10%	20%

*Midazolam: monoexponential decay; thiopental: biexponential.
†Meaningful estimate not available because of the small sample size.
‡Expressed as coefficient of variation.

Parameter estimates describing the plasma concentration profile in neonates after delivery (standard errors of estimates are in brackets).

The median time between induction of anesthesia and delivery (I-D interval) was 8.1 minutes in the thiopental group and 7.5 minutes in the midazolam group. The variation was large, with I-D values ranging from 4 to 14 minutes and 4 to 11 minutes, respectively. The difference was not statistically significant.

Aside from acidosis in two neonates excluded from the neurobehavioral study (2), no neonate had defects that might affect pharmacokinetics, and all 40 neonates are included in this study.

Placental Transfer (Table 1)

Thiopental. The median concentration in maternal plasma was 4.31 mg/liter, and the corresponding concentration in the umbilical vein was 4.65 mg/liter. The ratio between umbilical and maternal concentrations was 0.96, but with considerable variation (0.79 to 1.15). In 8 of 20 instances (40%), the ratio was >1 (that is, the umbilical vein concentration was above the maternal concentration).

Neither maternal nor umbilical concentrations correlated with I-D intervals ($P = 0.54$ and 0.13, respectively). However, there was a statistical significant correlation between maternal and umbilical concentrations ($P < 0.01$, $R = 0.66$, slope 0.58). The slope indicated rapid placental transfer. There was also no correlation between I-D interval and umbilical/maternal concentration ratios ($P = 0.98$).

Midazolam. The concentration of midazolam in one maternal sample was so high (7.6 mg/liter 22-fold higher than the median concentration) as to indicate a methodologic error and was thus excluded. In neonates, analysis of midazolam and α-hydroxymidazolam failed in four cases, three because of missing samples and one because of analysis failure.

The median maternal plasma concentration of midazolam at delivery was 339 μg/liter (re 234 to 614) and of α-hydroxymidazolam 22.0 μg/liter (re 11.8 to 50.8). The median umbilical venous concentrations were 318 μg/liter (re 188 to 411) and 5.0 μg/liter (re 3.0 to 9.1), respectively. The umbilical/maternal concentration ratio was 0.66 (re 0.50 to 1.05) with midazolam and 0.28 (re 0.12 to 0.48) with α-hydroxymidazolam. With midazolam 6 (33%) of 18 ratios were >1. Variation with the two benzodiazepines was greater than with thiopental.

Maternal midazolam concentrations correlated well with I-D interval ($P < 0.02$), but correlation of umbilical concentrations with I-D interval did not quite achieve statistical significance ($P = 0.06$). With α-hydroxymidazolam, significant correlation was found between I-D interval and umbilical concentrations ($P < 0.05$) and between maternal and umbilical concentrations ($P < 0.01$).

The ratios indicate a rapid placental transfer of midazolam, although not as rapid as with thiopental. α-Hydroxymidazolam was transferred somewhat more slowly.

Elimination

With thiopental, only one value sampled 13 hours after delivery was below detection limits. All other values obtained as long as 50 hours after delivery were above detection limits. Variation in levels was especially frequent during the first 8 hours.

Analysis of concentrations failed in two cases with midazolam because no samples were obtained. Midazolam could not be detected after 20 hours.

α-Hydroxymidazolam concentrations were low in all neonates. It was not detectable beyond 15 hours after delivery and a total of 29 (54%) of 53 samples were below detection level.

The results obtained in the NONMEM analysis are summarized in Table 2. The elimination half-life of midazolam averaged 6.3 hours, with a relatively large interindividual variability (38%) (that is, its value may vary from 3.3 to 12 hours). The population mean of the terminal half-life of thiopental was 14.7 hours. The sample of 20 neonates was too small to obtain meaningful estimates of the interindividual variability of all four parameters in the more complex biexponential model used for thiopental. The extrapolated plasma concentration at the time of delivery averaged 64.1 μg/liter for midazolam and 1.9 mg/liter for thiopental.

Discussion

Placental Transfer

Placental transfer of drugs is determined by many factors, including lipophilicity (4), technique of administration (6,10,18), and relation between uterine contractions and administration (19). In addition, when umbilical blood is used for determination of the concentrations in the newborn, one must bear in mind that the concentration of drug is greater in umbilical venous blood than in umbilical arterial blood (9) and neonatal blood (20). Furthermore, umbilical venous blood levels can reach values higher than maternal levels, a frequent finding with diazepam (21,22).

In this study, high umbilical/maternal plasma concentration ratios were found with thiopental, whereas the values were lower with midazolam and α-hydroxymidazolam. The high ratios suggest very rapid transfer of thiopental and a somewhat less rapid transfer of midazolam. The main metabolite of midazolam, α-hydroxymidazolam, has been found in concentrations similar to those of midazolam (16), but in this study, the concentrations of the metabolite in the neonates were relatively low, with umbilical/maternal ratios of approximately 0.3. One explanation may be a relatively slow placental transfer of α-hydroxymidazolam, perhaps due to a decrease in lipophilicity as a consequence of increased polarity of the metabolite in relation to midazolam. A low hepatic clearance of midazolam and α-hydroxymidazolam would further support this hypothesis. The relatively low maternal plasma concentrations of α-hydroxymidazolam may be a consequence of a short I-D interval, allowing only a limited maternal metabolism of midazolam.

A comparison of the results of this study with those of other studies shows that the umbilical/maternal ratio of midazolam appears to be lower than that of diazepam, suggesting that placental transfer of diazepam may be more rapid than that of midazolam (8,10,23). In only one earlier study has the placental transfer of midazolam been extensively studied (18). When given the night before delivery, midazolam could only be detected in umbilical vessels in 1 of 13 neonates. Administered as a premedicant on the day of delivery, the results, especially umbilical/maternal concentration ratios, were approximately the same as in our study.

Elimination

Elimination of drugs used in obstetric anesthesia is fraught with practical difficulties, including ethical considerations of drawing multiple blood samples from one neonate, of such a magnitude that the number of investigations is small indeed (3). In the present study, it was decided to use repeated samples from the neonates at different intervals, rather than totally relying on the interindividual comparisons because of large variation in plasma concentration. The small number of samples from each individual necessitated the use of population pharmacokinetics.

The population average of the terminal half-life was substantially higher for both midazolam and thiopental than the values found in adults (12,24,25). Similar to pharmacokinetic results in other populations (adults, children), the terminal half-life of thiopental was more than twice as long as that of midazolam. In addition, a clearly biphasic plasma concentration decrease with time was found for thiopental, whereas midazolam pharmacokinetics could be described under the assumption of a one-compartment model. The estimate of the interindividual variability of the midazolam half-life has to be interpreted with caution because the number of individuals probably was too small for a reliable estimate. This may be seen from the relatively large standard error of the estimate (25%) (Table 2). The sample size was too small to obtain meaningful estimates of the interindividual variance of the parameters in the two-compartment model for thiopental. The basic pharmacokinetics, total body clearance and volume of distribution, could not be determined in this study since the estimation would require direct administration of the compound to the neonate. Although such a study would allow the estimation of the complete pharmacokinetic profile, it would pose difficult ethical problems. In addition, we believe, that in the context of cesarean section anesthesia, the most relevant questions with respect to the pharmacokinetics in the neonate are the terminal half-life and the expected concentration in the neonates after delivery. Both questions could be addressed in this study.

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1989;68:243–8

Extent of Blockade with Various Approaches to the Lumbar Plexus

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PARKINSON SK, MUELLER JB, LITTLE WL, BAILEY SL. Extent of blockade with various approaches to the lumbar plexus. Anesth Analg 1989;68:243–8.

The extent of blockade when four different techniques were used for blocking the lumbar plexus was prospectively evaluated in 80 adult patients. The extent of blockade was measured by testing motor function of all nerves except the lateral and posterior femoral cutaneous nerves, which were evaluated by pinprick response. The posterior approaches of Dekrey at L_3 ($n = 20$) and Chayen at L_{4-5} ($n = 20$) proved similarly effective in producing blockade of the femoral, obturator, and lateral femoral cutaneous nerves, as well as the nerves to the psoas muscle. The anterior approach of Winnie (femoral sheath or 3-in-1 block) using paresthesia ($n = 20$) or peripheral nerve stimulation ($n = 20$) proved effective in producing blockade of the femoral and lateral femoral cutaneous nerves, but ineffective for obturator nerve blockade. None of the four techniques produced blockade of the sacral plexus. Perhaps our means of assessing blockade (motor) is what produced the difference between our findings and those of others.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—lumbar plexus block.

Introduction

One anterior and at least two posterior approaches to the lumbar plexus have been described. Winnie (1) described the inguinal paravascular technique (3-in-1 block) and stated that it routinely blocks the femoral, lateral femoral cutaneous (LFC), and obturator nerves when 20 ml or more of anesthetic solution is used. Dekrey* described the use of a posterior approach to the psoas muscle sheath at the level of L_3 for lumbar plexus blockade. Chayen (2), Winnie (3), and Dekrey all describe another posterior approach with the placement of the needle tip into the fascial compartment between the psoas and the quadratus lumborum muscles at approximately the level of the L_{4-5} interspace (psoas compartment or lumbosacral plexus block). Winnie and Dekrey claim that the L_{4-5} approach provides complete sacral blockade as well as block of the lumbar plexus. Chayen reports the need to combine the L_{4-5} (lumbosacral) block with a sciatic nerve block to provide complete anesthesia of the lower extremity. Previous clinical experience by the authors has failed to corroborate Winnie's results with his inguinal paravascular approach regarding obturator nerve block. Because of the disparity regarding utility of the anterior approach and the uncertainty surrounding the extent of sacral blockade using the posterior approaches, a prospective study was undertaken in adults of the extent of neural blockade when the two posterior approaches (at L_3 and L_{4-5}) and the femoral sheath approach (with paresthesia and with peripheral nerve stimulation) were employed.

Methods

The Posterior Approach at L_3 (psoas sheath block).

The first four lumbar nerves emerge through the lateral foramina of the vertebral column and enter the substance of the psoas muscle, where the lumbar

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

* Editor's note: A citation to the literature is not possible. Dr. John Dekrey was a U.S. Navy anesthesiologist widely recognized and respected as a teacher of and a skillful practitioner of regional anesthesia—"The Wizard of the Needle." His techniques for blocking the lumbar plexus were, however, not reported in print, and so remain unavailable to all except those whom he has trained. His contributions and his ability in regional anesthesia warrant acknowledgment even in the absence of published articles.

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plexus is usually formed (4). The fifth lumbar nerve emerges below the origin of the psoas muscle. The psoas muscle arises from caudal borders of the transverse processes of all lumbar vertebrae, from sides of bodies of corresponding intervertebral disks, and from a series of tendinous arches from the bodies of the lumbar vertebrae (5). The psoas muscle is enclosed in a sheath that readily confines spread of an anesthetic solution. Since the lumbar plexus is formed within the substance of the psoas muscle, local anesthetic solution injected into the muscle should result in lumbar plexus blockade. Because of this, Dekrey used a technique in which the tip of the needle was placed in the psoas muscle at the level of L_3. The patient is placed in the lateral position, hips flexed, with the side to be blocked uppermost. A 20-gauge, 9-cm (3 1/2-inch) spinal needle is inserted 3–4 cm lateral to the spinous process of L_3 and directed slightly cephalad (but not medially or laterally) to contact the transverse process of L_3. After touching the process, the needle is then redirected caudad to the transverse process and advanced 1.5 cm deeper. This places the tip of the needle in the psoas muscle. We modified the approach by using a peripheral nerve stimulator to elicit a quadriceps femoris muscle twitch, indicative of close proximity to the lumbar plexus.

The Posterior Approach at L_{4-5} (psoas compartment or lumbosacral plexus block).

At the level of L_{4-5} the nerves of the lumbar plexus to the lower extremity have emerged from the psoas muscle and lie in a fascial compartment between the psoas and quadratus lumborum muscles. Local anesthetic injected into the potential space between these two muscles at this level should bathe the lumbar plexus (and possibly the sacral plexus). Chayen (2), Winnie (3), and Dekrey all used this approach or slight modifications of it. With Chayen's psoas compartment approach the patient is placed in the same position as for the L_3 approach described above. A 20-gauge, 9-cm (3 1/2-inch) spinal needle is inserted perpendicular to the coronal plane at a point 3 cm caudad to the intercristal line and 4–5 cm lateral to the midline. If the transverse process of L_5 is encountered, the needle is redirected cephalad to it. Winnie's description (needle inserted at the intersection of the intercristal line and a line drawn parallel to the spine through the posterior superior iliac spine) places the needle tip in approximately the same position—about 4–5 cm from the midline, between the transverse processes of L_4 and L_5, and in the potential space between the quadratus and the psoas. Dekrey's technique places the needle caudad to the transverse process of L_4, about 4 cm from midline, and in the same fascial compartment as that of Winnie's and Chayen's approaches. A loss of resistance technique can be used to confirm passage of the needle tip through the anterior fascia of the quadratus lumborum. Confirmation of the placement of the needle tip in the plexus was observed by using a peripheral nerve stimulator, looking for a quadriceps muscle twitch (femoral nerve).

The Anterior or Femoral Sheath Approach.

At the level of the inguinal ligament, the femoral nerve is bounded laterally by the fascia of the iliacus muscle, medially by the fascia of the psoas major muscle, and anteriorly by the transversalis fascia. Winnie's inguinal paravascular technique (1) of lumbar plexus block utilizes the fascial envelope around the femoral nerve as a conduit which carries injected anesthetic up to the level where the lumbar plexus is located between the quadratus lumborum and the psoas major muscles. With the patient supine, a 22-gauge, 4-cm (1 1/2-inch) short-bevel needle is inserted just caudad to the inguinal ligament and lateral to the femoral artery. The needle is directed cephalad and a femoral nerve paresthesia (or quadriceps twitch using the nerve stimulator) is used to confirm correct placement. The local anesthetic is then injected while applying digital pressure distal to the needle to assure that the injected solution moves cephalad towards the lumbar plexus and not distally.

After institutional approval and informed consent, 80 patients ASA physical status 1 and 2 scheduled for lower extremity surgery were randomly assigned to one of four groups ($n = 20$ in each). Ages ranged from 19 to 49 years, and weight from 50 to 116 kg. The four techniques used in the 4 groups were: (1) the posterior L_3 approach to the lumbar plexus; (2) the posterior approach at L_{4-5}; (3) the femoral approach using paresthesias; and (4) the femoral approach using peripheral nerve stimulation.

All procedures used an immobile needle technique. For the anterior approaches, 22-gauge, 4-cm (1 1/2-inch) short-bevel needles were used. For the posterior approaches, 20-gauge, 9-cm (3 1/2-inch) spinal needles were used, with the exception of two patients in whom 13-cm (5-inch) needles were required to reach the appropriate depth. All needles were uninsulated. The local anesthetic solution was a mixture of 1% lidocaine and 0.2% tetracaine with 1: 200,000 epinephrine. In each patient 0.5 ml/kg of the

Table 1. L_3 Approach: Evaluation of Somatic Nerve Function as a Measure of Blockade of the Lumbar Plexus at 5, 15, and 30 Minutes (n = 20)

	5 min	15 min	30 min
Knee extension (femoral nerve)[a]	2[b] (16)[c]	9 (11)	20
Hip adduction (obturator nerve)	1 (18)	12 (8)	20
Lateral midthigh sensation (LFC)[d]	4 (13)	12 (7)	19 (0)
Hip flexion (nerves to psoas and femoral nerve)	5 (14)	11 (9)	20
Hip abduction (superior gluteal nerve)	0 (0)	0 (3)	0 (4)
Dorsiflexion of foot (peroneal nerve)	0 (0)	0 (1)	0 (3)
Plantar flexion of foot (tibial nerve)	0 (0)	0 (1)	0 (2)
Posterior mid-thigh sensation (PFC)[d]	0 (0)	0 (0)	0 (0)

[a] Inability to perform these movements is indicative of blockade of the listed nerves.
[b] Numbers without parentheses indicate number of patients with complete impairment (paralysis or lack of sensation) of the indicated function.
[c] Numbers with parentheses indicate number of patients with partial impairment (paresis or decreased sensation).
[d] LFC, lateral femoral cutaneous nerve; PFC, posterior femoral cutaneous nerve.

solution was injected, regardless of the approach used. A Neuro Technology DigiStim II peripheral nerve stimulator with variable output was used to provide one impulse per second. Only patients with normal sensory and motor function of the lower extremities were included in the study. Blockade was assessed in all nerves by testing motor function, except for the lateral and posterior femoral cutaneous nerves (LFC and PFC, respectively), which were evaluated by pinprick response. The following nerves were evaluated 5, 15, and 30 minutes after injection of the anesthetic solution: tibial (L_{4-5}, S_{1-3}): plantar flexion of the foot; peroneal (L_{4-5}, S_{1-2}): dorsiflexion of the foot; femoral (L_{2-4}): knee extension; obturator (L_{2-4}): hip adduction; superior gluteal (L_{4-5}, S_1): hip abduction; nerves to the iliopsoas (L_{2-3} and femoral): hip flexion; LFC (L_{2-3}): lateral mid-thigh sensation; and PFC (S_{1-3}): posterior midthigh sensation. Hip adduction was assessed with the patient supine, hips and knees flexed, with the patient asked to keep his knees "pinched" together while the examiner attempted to separate the knees. This effectively isolates the adductor group innervated by the obturator nerve. Hip abduction (gluteus medius and minimus muscles and tensor fascia lata via the superior gluteal nerve—L_{4-5}, S_1) was tested with the patient supine, knees extended and together. The examiner then applied force to the lateral aspect of the patient's knees while asking the patient to separate his knees. The rating scale for motor blockade was: 0, normal contraction or strength; 1, reduced contraction (paresis); and 2, no contraction (paralysis). Sensory blockade to pinprick was determined using a rating scale of: 0, sharp; 1, dull or decreased sensation; and 2, no sensation. Only blocks which resulted in femoral nerve blockade (quadriceps muscle paralysis) by 30 minutes were included in the study, as femoral nerve (quadriceps) stimulation was used to confirm needle placement for three of the four approaches. Stimulation of the femoral nerve was used to optimize placement for the posterior approaches, because the femoral nerve lies between the obturator nerve (medial) and lateral femoral cutaneous nerve (lateral) in the plexus. Care was taken to correctly identify knee extension (quadriceps muscle contraction via femoral nerve stimulation) rather than proximal thigh movement or hip flexion (direct psoas muscle stimulation). Injections resulting in bilateral (epidural) anesthesia were not included in the study because of the difficulty in assessing the progression of plexus blockade in such cases.

The statistical significance of difference in frequencies of the blockade of individual nerves following different approaches (posterior vs posterior and anterior vs anterior) was determined using the χ-^{2} test. Differences were considered significant at $P < 0.05$.

Results

Tables 1–4 show the progression of blockade for each approach at 5, 15, and 30 minutes postinjection. As can be seen, both posterior approaches were found effective in producing blockade of the femoral, obturator, and LFC nerves. In addition, the nerves to the psoas were reliably blocked. No statistical difference was found between the two posterior approaches when individual nerve blockade at 30 minutes was compared. None of the approaches (posterior or anterior) resulted in complete sacral plexus blockade. However, in some patients the posterior approaches caused partial blockade in those nerves receiving contributions from the lumbosacral trunk (L_{4-5}). Complete block of any nerve with a component from S_1, S_2, or S_3 was never achieved. No complications from neural blockade were found in patients from any of the groups (anterior or posterior).

Contrary to what has been described previously (1), the anterior approach (femoral) resulted in block-

Table 2. L_{4-5} Approach: Evaluation of Somatic Nerve Function as a Measure of Blockade of the Lumbar Plexus at 5, 15, and 30 Minutes (n = 20)

	5 min	15 min	30 min
Knee extension (femoral nerve)	8 (10)	15 (5)	20
Hip adduction (obturator nerve)	7 (10)	15 (5)	20
Lateral mid-thigh sensation (LFC)	5 (15)	17 (3)	19 (1)
Hip flexion (nerves to psoas and femoral nerve)	8 (11)	17 (3)	17 (3)
Hip abduction (superior gluteal nerve)	0 (0)	0 (3)	0 (5)
Dorsiflexion of foot (peroneal nerve)	0 (0)	0 (2)	0 (5)
Plantar flexion of foot (tibial nerve)	0 (0)	0 (1)	0 (4)
Posterior mid-thigh sensation (PFC)	0 (0)	0 (0)	0 (0)

See Table 1 for abbreviations.

Table 3. Femoral Approach with Paresthesia: Evaluation of Somatic Nerve Function as a Measure of Blockade of the Lumbar Plexus at 5, 15, and 30 Minutes (n = 20)

	5 min	15 min	30 min
Knee extension (femoral nerve)	6 (11)	15 (5)	20
Hip adduction (obturator nerve)	0 (0)	0 (1)	0 (2)
Lateral mid-thigh sensation (LFC)	1 (17)	12 (8)	19 (1)
Hip flexion (nerves to psoas and femoral nerve)	0 (8)	0 (17)	1 (18)
Hip abduction (superior gluteal nerve)	0 (0)	0 (0)	0 (0)
Dorsiflexion of foot (peroneal nerve)	0 (0)	0 (0)	0 (0)
Plantar flexion of foot (tibial nerve)	0 (0)	0 (0)	0 (0)
Posterior mid-thigh sensation (PFC)	0 (0)	0 (0)	0 (0)

See Table 1 for abbreviations.

Table 4. Femoral Approach with Nerve Stimulation: Evaluation of Somatic Nerve Function as a Measure of Blockade of the Lumbar Plexus at 5, 15, and 30 Minutes (n = 20)

	5 min	15 min	30 min
Knee extension (femoral nerve)	6 (11)	14 (6)	20
Hip adduction (obturator nerve)	0 (0)	0 (1)	0 (1)
Lateral mid-thigh sensation (LFC)	2 (14)	9 (11)	17 (3)
Hip flexion (nerves to psoas and femoral nerve)	0 (8)	0 (11)	0 (13)
Hip abduction (superior gluteal nerve)	0 (0)	0 (0)	0 (0)
Dorsiflexion of foot (peroneal nerve)	0 (0)	0 (0)	0 (0)
Plantar flexion of foot (tibial nerve)	0 (0)	0 (0)	0 (0)
Posterior mid-thigh sensation (PFC)	0 (0)	0 (0)	0 (0)

See Table 1 for abbreviations.

ade of only the femoral and LFC nerves. Motor blockade of the obturator nerve was not produced using the anterior approach. There was no statistical difference in the results from the two groups of femoral approach techniques (paresthesia vs femoral nerve stimulation) when results of complete blockade at the end of thirty minutes were evaluated for each nerve.

The L_3 approach was attempted in 27 patients. In two patients a quadriceps muscle twitch could not be elicited, so an L_{4-5} approach was then attempted (successfully on both occasions). Four of the 25 patients in whom a quadriceps muscle response was elicited when using the L_3 approach developed epidural blockade within 30 minutes (ranging from T_{12} to T_6 for cephalad extent of bilateral loss of sensation). These patients were excluded from the study. After regression of the epidural anesthesia, each of the 4 patients continued to have residual plexus blockade (indicating correct placement of the needle). One of the 25 patients in whom the L_3 approach was used (with femoral nerve stimulation) failed to develop complete femoral nerve blockade at the end of the 30-minute observation period and was also excluded from the study.

The L_{4-5} block was performed in 23 patients. One of the 23 L_{4-5} blocks resulted in epidural anesthesia to T_{10} (upper level of bilateral sensory deficit) and was excluded from the study. This patient had residual plexus blockade after regression of the epidural anesthesia. Two of the patients receiving L_{4-5} blocks failed to have complete femoral nerve blockade within 30 minutes, in spite of an appropriate quadriceps twitch to confirm needle placement, and were also excluded from the study.

Discussion

The results obtained indicate that the two posterior approaches which were evaluated are effective in producing blockade of the nerves from the lumbar plexus that innervate the lower extremity. Hip flexion is also abolished with these two approaches. The muscles responsible for hip flexion are the psoas (innervated by nerves directly from L_{2-3}) and the iliacus (innervated by the femoral nerve). However, no evidence was found that the sacral plexus can be reliably blocked with the posterior approaches to the lumbar plexus. Although the lumbosacral trunk may occasionally be blocked with the posterior approaches, a sciatic nerve block will still be required to achieve complete anesthesia of the lower extremity. Dalens (6) found the posterior approach of Winnie (L_{4-5}) to be effective for both the lumbar and sacral plexus in children (evaluation was done postoperatively). However, no motor blockade was observed in areas supplied by the sciatic nerve and none of the surgeries involved the lower leg or foot. Thus, it appears that the posterior approach may not reliably block the sacral plexus in children. This is consistent with our findings in adults.

Both the L_3 and L_{4-5} approaches can result in epidural blockade. This has been noted before (7). Dalens found this in children when using a modified Chayen (L_{4-5}) approach. The epidural anesthesia is most likely due to spread of the local anesthetic solution proximally into the paravertebral space (8), rather than from needle placement directly into the epidural space. All of the patients with epidural blockade had residual plexus anesthesia when the epidural anesthesia wore off. Although the pathway or mechanism for epidural blockade from lumbar plexus injection has not been definitively established, the fact remains that epidural anesthesia may occur, and thus preservative-free solution should be used and the patient fully monitored and observed for evidence of epidural blockade.

The modified Chayen (L_{4-5}) approach used by Dalens (6) is a significant change (more medial) from that of the original description (2). Dalens' modified approach results in lumbosacral trunk stimulation (flexion–extension movements of the ankle and toes) when a peripheral nerve stimulator is used and a very high incidence of epidural block (23 of 25 patients). The lumbosacral trunk (L_{4-5}) is the most medial component of the lumbar plexus and the closest to the paravertebral space. It is not surprising that large volumes of local anesthetic deposited close to the paravertebral space can result in epidural block. The best nerve to stimulate in blocking the lumbar plexus is the femoral nerve (quadriceps femoris muscle twitch), as it is located in the middle of the plexus, bounded on either side by the LFC (lateral) and obturator (medial) nerves.

The femoral approach (3-in-1), with paresthesia as well as with nerve stimulation, was found effective for LFC and femoral nerve blockade, but it routinely spared the obturator nerve. It appears that although the local anesthetic can travel sufficiently proximal (or lateral) between the psoas and the iliacus to block the LFC, it does not travel proximally far enough in sufficient quantity to block the obturator nerve. The volumes of local anesthetic (0.5 ml/kg) that were used were even larger than those used by Winnie in the original description of the technique. He stated that if a volume of 20 ml or more is used, then anesthesia of the LFC, femoral, and obturator nerves is assured. It was not stated how the patients were assessed for block of the obturator nerve. The cutaneous sensory component of the obturator nerve is variable in its distribution, if present at all (9). We have seen many patients with intact obturator nerve function (hip adduction), but with complete lack of medial thigh sensation after LFC, sciatic, and low-volume femoral nerve blocks. The only way to effectively evaluate the obturator nerve function is to assess hip adduction. Placing the patient supine, with both hips and knees flexed, and asking the patient to pinch his knees together while the examiner attempts to pull them apart is an easy and reliable test for isolated hip adduction. The patient with complete obturator nerve blockade will be unable to hold his knees together and the affected lower extremity will flop to the side. The obturator nerve has two divisions, anterior and posterior. Both carry motor fibers, but only the anterior division provides any cutaneous innervation. The posterior division is important in that it contributes to innervation of the knee joint. If not blocked, it can also result in ischemic pain of the adductor muscle group if tourniquet time is prolonged.

Two cases have been reported of inadvertent 3-in-1 block following injection of the lateral femoral cutaneous nerve (10,11). Neither case resulted in complete paralysis of hip adduction. Therefore, it is doubtful that the obturator nerve was blocked in either case. Slight paresis of hip adduction may be seen after femoral nerve block, as it innervates the pectineus muscle, one of the weak adductors of the thigh (12).

The two femoral sheath approaches, seeking paresthesias and using nerve stimulation, were equally effective in assuring block of the LFC and femoral nerves. The use of a nerve stimulator decreases patient discomfort (heavy analgesia/sedation or general anesthesia may be used), and may be associated with less neural trauma than when paresthesias are sought (13). Since the results when using paresthesias and nerve stimulation are similar, the use of a peripheral nerve stimulator is advocated to perform the femoral sheath block.

As mentioned above, several patients failed to achieve complete motor blockade of the femoral nerve at 30 minutes when the posterior approaches were used, in spite of obtaining adequate quadriceps muscle response to lumbar plexus (femoral nerve) stimulation. Perhaps this problem could be rectified by using insulated needles, allowing more precise needle placement.

In summary, we found the posterior approaches to the lumbar plexus (at L_3 and at L_{4-5}) effective in producing blockade of the nerves to the lower extremity from the lumbar plexus (femoral, LFC, and obturator), but not effective in blocking nerves from the sacral plexus (tibial, peroneal, and posterior femoral cutaneous). The anterior (femoral sheath) approach, both with paresthesia and with peripheral nerve stimulation, was effective in blocking the femoral and LFC nerves, but routinely spared the obturator nerve. With this understanding of the extent of neural blockade with the various approaches, lumbar plexus blocks can effectively be used in combination with sciatic (and obturator, if needed) nerve blocks, or as an adjunct to general anesthesia for procedures involving the lower extremity.

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Comparison of Sedative Infusions During Regional Anesthesia—Methohexital, Etomidate, and Midazolam

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URQUHART ML, WHITE PF. Comparison of sedative infusions during regional anesthesia—methohexital, etomidate, and midazolam. Anesth Analg 1989;68:249–54

Using a randomized, double-blind study design, the intra- and postoperative sedative effects of three intravenous central nervous system depressants were compared in 64 patients during regional anesthesia. After establishing regional anesthesia, methohexital 59 ± 29 mg IV, etomidate 12.6 ± 8 mg IV, or midazolam 3.7 ± 1.5 mg IV (mean dose ± SD) were infused in a titrated fashion over 5–15 minutes to achieve similar end points of sedation. This level of sedation was then maintained with a variable-rate infusion of either methohexital 180 ± 65 mg/hr, etomidate 32 ± 12 mg/hr, or midazolam 7.5 ± 4 mg/hr (mean dose ± SD) To maintain a stable level of sedation, changes in the maintenance infusion rate were required more frequently with methohexital (4.6 ± 3 times) than with etomidate (2.6 ± 2 times) or midazolam (2.7 ± 3 times). Decreases in oxygen saturation below 95% were more frequent with midazolam than with methohexital and etomidate, while recall of intraoperative events was less frequent after midazolam. Observer evaluations found less sedation in the methohexital and etomidate groups than in the midazolam group during the early postoperative period. However, the patients' evaluation of residual sedative effects (e.g., postoperative sedation visual analogue scores) and discharge times from the recovery room were similar in all three groups. Nevertheless, patients given midazolam had significantly greater impairment of performance on the digit–symbol substitution test in the early postoperative period than did patients given either methohexital or etomidate.

Key Words: ANESTHETICS, INTRAVENOUS—methohexital, etomidate, midazolam. ANESTHETIC TECHNIQUES, REGIONAL ANESTHESIA—sedation.

Regional anesthesia can offer advantages over general anesthesia for many surgical patients. Intravenous (IV) sedative and analgesic medication are useful adjuvants during regional anesthesia because the operating room is an anxiety-provoking environment, positioning for surgery can be uncomfortable, and spontaneous movement by an inadequately sedated patient can interfere with the operation (1). The intermittent bolus administration of intravenous sedative-hypnotic and analgesic drugs is the most widely used technique for producing intraoperative sedation in this situation. Excessive doses of these drugs can, however, produce significant respiratory depression and may contribute to a delayed recovery and discharge after outpatient procedures (2). In a closed claims analysis of factors contributing to unexpected cardiac arrests during regional anesthesia, intravenous sedation was one of the factors that may have contributed to the adverse outcomes (3).

Use of continuous IV infusions of anesthetic and analgesic drugs has been found to be associated with fewer intraoperative side effects and shorter recovery times than the traditional intermittent bolus technique (4,5). The purpose of this study was to compare the efficacy of methohexital, etomidate, and midazolam in terms of their ability to produce a stable level of sedation without cardiorespiratory depression when given by a continuous variable-rate infusion technique. In addition, we compared the amnestic properties, postoperative recovery of psychomotor function, and side effects of these three sedative-hypnotic drugs.

Materials and Methods

Sixty-four unpremedicated adult patients, ASA physical status I–III, who had agreed to regional anesthe-

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sia for pelvic, urologic, or extremity surgery, were studied after giving their written informed consent. The study protocol was approved by the Committee for the Protection of Human Subjects at Stanford University. Patients were randomly assigned to receive either methohexital, etomidate, or midazolam during the operation according to a double-blind protocol design.

Preoperatively, patients completed three different 100-mm visual analog scales (VAS) to determine their baseline level of sedation (0 = wide awake to 100 = almost asleep), anxiety (0 = calm to 100 = extremely anxious), and pain (0 = none to 100 = severe). A digital–symbol substitution test (DSST) was used to assess their baseline level of cognitive function. The DSST involves the rapid recognition and matching of ten random single digits and symbols. The score of the test was the number of correct substitutions performed in 90 seconds. Finally, a blinded observer evaluated the baseline level of sedation of each patient according to the following scale: 0 = awake and anxious; 1 = awake and alert with minimal anxiety; 2 = calm and drowsy with eyes open; 3 = mild sedation, resting comfortably with eyes closed but responsive to verbal stimuli; 4 = moderate sedation, unresponsive to verbal stimuli but responsive to gentle tactile stimuli; and 5 = profound sedation (hypnosis), unresponsive to tactile stimuli.

After the preoperative VAS and DSST studies were completed, patients were taken to the operating room where baseline measurements of blood pressure and heart rate were made and the level of sedation was assessed by a "blinded" observer. Monitors included a Dinamap automatic blood pressure cuff, an ECG, and a Nellcor pulse oximeter. Fentanyl 50 μg (1 ml) IV was administered for analgesia immediately before initiating the regional block procedure. The choice of the regional technique was at the discretion of the attending anesthesiologist and consisted of spinal, epidural, or axillary nerve block procedures. All patients were given supplemental oxygen, 4–6 L/min, via nasal prongs.

Five minutes after injecting the local anesthetic solution, the onset of analgesia was established, and a loading infusion of the intravenous sedative solution was administered over 5–15 minutes using a calibrated syringe infusion pump. Based on their potency as induction agents (6), equipotent solutions of the three study drugs (methohexital 8.33 mg/ml, etomidate 2.0 mg/ml, or midazolam 0.67 mg/ml) were infused at an initial rate of 36 ml/hr. This infusion rate was continued until patients achieved a sedation level of 3 on the observer's rating scale (i.e., resting comfortably with eyes closed, but responsive to voice commands), at which time the infusion rate was decreased to 9 ml/hr and subsequently varied to maintain this level of sedation during the entire procedure. Mean arterial pressure, heart rate, arterial oxygen saturation, and sedation scores were recorded every minute during the initial infusion period and subsequently at 5–10-minute intervals throughout the operation. Intraoperative side effects and requirements for supplemental medications were also recorded. The sedative infusion was discontinued at the end of the operation (i.e., upon removal of the surgical drapes).

Upon arrival in the postanesthesia care unit (PACU), each patient's sedation score was reassessed, and both the VAS and DSST were repeated. These tests were subsequently repeated every 30 minutes after discontinuation of the sedative infusion until the patient was discharged from the PACU. Criteria for discharge included a return to preoperative (baseline) mental status, hemodynamic stability, and absence of residual neural blockade and side effects (e.g., nausea, bleeding, pain). All postoperative side effects and medications administered in the PACU were recorded. Upon discharge from the PACU, patients completed a questionnaire assessing their level of satisfaction (if any) with the anesthetic technique, recall of perioperative events, and postoperative complaints (Appendix 1). Patients completed a similar questionnaire 1 week after the surgical procedure.

Data were analyzed with the Systat statistical program using one-way ANOVA (analysis of variance), the χ^2 test, and the Kruskal–Wallis test (for nonparametric data). Temporal changes in the VAS and DSST recovery tests were evaluated using repeated measures of analysis of variance. Data are presented as mean values ± SD, with P values <0.05 considered statistically significant.

Results

Demographic data from the 64 patients studied are summarized in Table 1. The three study groups were comparable with respect to age, preoperative sedation, anxiety and DSST scores, and time required to perform the regional anesthesia, as well as the upper sensory level of the block (for spinal and epidural blocks).

The sedative drug dosages required to achieve a sedation score of 3 and the average infusion rate required to maintain this level of sedation are summarized in Table 2. There were no significant differ-

Table 1. Demographic Characteristics in Three Study Groups

	Midazolam	Methohexital	Etomidate
Number (*n*)	21	22	21
Age (yr; mean ± SD)	60 ± 95	5 ± 14	60 ± 18
Weight (kg; mean ± SD)	84 ± 11	79 ± 15	72 ± 18*
Outpatients (%)	27	41	43
Male (%)	95	91	67*
Prior anesthetics			
General (%)	90	73	90
Regional (%)	43	45	52
Regional technique			
Spinal (%)	100	86	81*
Epidural (%)	0	14	14
Axillary (%)	0	0	5
Time to initiate block (min)	14.0 ± 6	13.5 ± 4	14.4 ± 6
Highest level† (dermatome) (mean ± SD)	T6 ± 2	T6 ± 2	T5 ± 3
Duration of operation (min; mean ± SD)	52 ± 26	79 ± 62	50 ± 38

*Significantly different from midazolam group, $P < 0.05$.
†With epidural and spinal anesthesia only.

Table 2. Loading Dose and Maintenance Dosage Requirements, as Well as Infusion Times for the Three Treatment Groups*

	Midazolam	Methohexital	Etomidate
Loading			
Time (min)	10 ± 4	12 ± 5	10 ± 5
Dose (mg)	3.7 ± 1.5	59 ± 29	12.7 ± 8
Maintenance			
Time (min)	53 ± 28	77 ± 57	49 ± 41
Rate (ml/hr)	11.2 ± 6.2	21.5 ± 8.0†	16.0 ± 6.2†
Rate (mg/hr)	7.5 ± 4	180 ± 65	32 ± 12
Rate changes (*n*)	2.7 ± 3	4.6 ± 3*	2.6 ± 2

*Mean values ± SD.
†Significantly different from midazolam group, $P < 0.05$.

ences among the three treatment groups in the times for the loading infusions (and volumes administered) to achieve a sedation level of 3 on the observer's scale. Maintenance infusion rates with etomidate were significantly higher than with midazolam, while patients given methohexital required an infusion rate significantly higher than that needed by patients in either of the other two study groups. In addition, the use of methohexital required significantly more frequent adjustments in the maintenance infusion rate than did the use of either etomidate or midazolam infusions. The sedation efficacy score (defined as the percentage of observation periods in which the patient had a sedation score of 3) did not differ significantly among the three treatment groups (Table 3).

Intraoperatively, there were no differences among treatment groups with respect to mean arterial pressure (MAP) and heart rate (HR) (Figs. 1 and 2). During the time between the induction of regional anesthesia and the start of the maintenance infusion, there were statistically significant decreases in MAP and HR in all three groups. The magnitude of these changes was related to the preoperative MAP and the dermatomal level achieved with the spinal or epidural anesthetic ($P < 0.05$) but was unrelated to the study medication. There was no difference among the drug treatment groups with respect to requirements for ephedrine or atropine to treat hypotension and bradycardia, respectively. Despite carefully titrating the three study medications to achieve the same clinical end point, patients receiving midazolam had a significantly higher incidence of episodes of arterial oxygen desaturation below 95% saturation (38%) than did patients given etomidate (5%) or methohexital (19%) (Table 4). All episodes of desaturation responded promptly to stimulation of the patient, and no patient required instrumentation of their airway or assisted ventilation. In contrast to midazolam and methohexital, two patients in the etomidate group complained of pain on injection, and two others developed myoclonus during the initial (loading) infusion.

Recovery from the central nervous system (CNS) effects of the three study medications is summarized in Table 3 and in Figures 3–5. A significantly higher percentage of patients receiving methohexital or etomidate during surgery were considered to be awake and alert by the blinded observer (i.e., sedation score of 1) upon entering the PACU compared to the midazolam group. Except for an increased anxiety score at 30 minutes after discontinuation of the etomidate infusion, there were no significant differences among the three groups with respect to the patient-assessed sedation and anxiety VAS scores (Figs. 3 and 4). Residual sedation was not the limiting factor in determining the discharge time from the PACU. However, patients given midazolam had significantly greater impairment of performance on the DSST upon arrival in the PACU and throughout the recovery period (Fig. 5). Although there was a higher incidence of headaches in the etomidate group, incidences of other postoperative side effects were similar in the three drug groups. In addition, no significant differences were noted between the groups with regard to postoperative analgesic requirements or discharge times from the PACU (Tables 3 and 4).

Assessment of the patient's ability to recall perioperative events revealed that significantly fewer patients given midazolam could recall intraoperative events (Table 5). Follow-up questionnaires revealed no difference in postdischarge complaints between patients in the three study groups. Patients in all three treatment

Table 3. Observer's Sedation Scores during and after Operation, as Well as PACU Discharge Times for the Three Treatment Groups

	Midazolam	Methohexital	Etomidate
Efficacy score*	93 ± 12	84 ± 14	83 ± 21
Time from end infusion to PACU arrival (min)	8 ± 3	8 ± 3	8 ± 3
Sedation scores in PACU arrival	2.2 ± 0.6	1.5 ± 0.5*†	1.8 ± 0.6*†
30 min	1.4 ± 0.6	1.0*	1.4 ± 0.6
60 min	1.2 ± 0.4	1.0	1.2 ± 0.6
90 min	1.0 ± 0.2	1.0	1.0
Discharge time (min)	143 ± 58	137 ± 80	129 ± 56

*Percentage of time during the operation that the patient was considered adequately sedated (observer's score = 3).
†Significantly different from the midazolam group, $P < 0.05$.

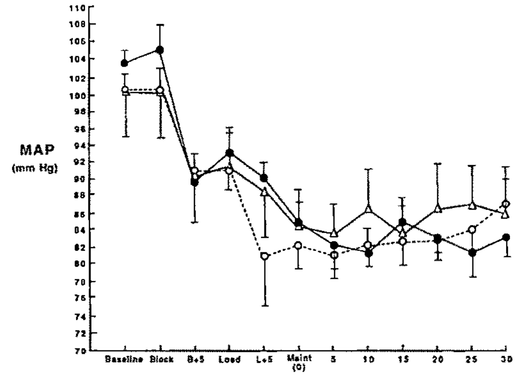

Figure 1. Mean arterial pressure (MAP) during and 5 minutes after regional anesthesia (Block, B+5), during and 5 minutes after loading infusion of sedative medication (Load, L+5), and time after starting maintenance sedative infusion. Treatment groups included (○) methohexital, (△) etomidate, and (●) midazolam. Data are presented as mean values ± SEM.

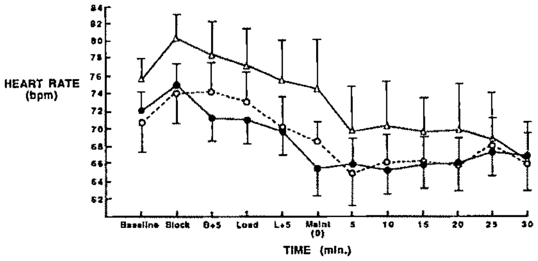

Figure 2. Heart rate (HR) during and 5 minutes after regional anesthesia (Block, B+5), during and 5 minutes after loading infusion of sedative medication (Load, L+5) and time after starting maintenance sedative infusion. Treatment groups included (○) methohexital, (△) etomidate, and (●) midazolam. Data are presented as mean values ± SEM.

groups reported that they were highly satisfied with their anesthesia. With the exception of one methohexital-treated patient, all patients stated that they were adequately sedated during surgery.

Discussion

Intravenous sedation during regional anesthesia increases patient acceptance of the technique by providing anxiolysis, supplemental analgesia, and lack of awareness (or amnesia) during the surgical procedure (1). The use of continuous intravenous infusion techniques for administering rapid and short-acting sedative drugs can improve the precision with which these compounds are administered and can provide for a more rapid recovery after the operation (4,5). Our current results demonstrate that the use of a variable-rate infusion of sedative-hypnotic drugs is effective in producing a stable level of intraoperative

Table 4. Incidence of Perioperative Side Effects in the Three Treatment Groups

	Midazolam	Methohexital	Etomidate
Intraoperative (%)			
pain on injection	0	0	10
myoclonus	0	0	10
nausea	14	5	10
0_2 sat. <95%	38	19*	5*
Recovery room (%)			
nausea	14	14	29
vomiting	5	9	5
antiemetic required	5	10	20
headache	0	9	19*
Postdischarge (%)			
nausea	19	18	43
vomiting	14	9	24
dizziness	29	18	33

*Significantly different from midazolam group, $P < 0.05$.

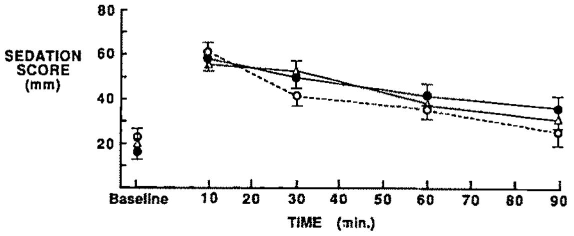

Figure 3. Level of sedation as determined by the patient using visual analogue scales (0 = no sedation to 100 = maximum sedation) before (baseline) and at various time intervals after methohexital (○), etomidate (△), or midazolam (●) administration. Data are presented as mean values ± SEM.

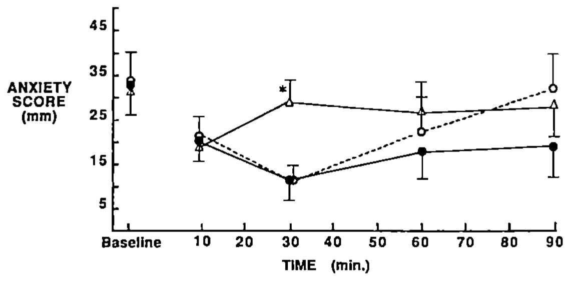

Figure 4. Level of anxiety as determined by the patient using visual analogue scales (0 = calm to 100 = extremely anxious) before (baseline) and at various time intervals after (○) methohexital, (△) etomidate, or (●) midazolam. Data are presented as mean values ± SEM.

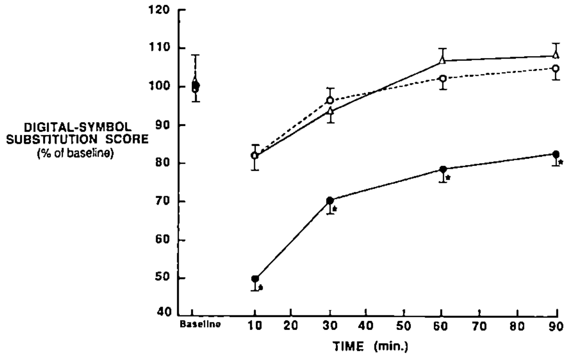

Figure 5. Changes in cognitive function expressed as a percentage of the preoperative (baseline) score on the digit–symbol substitution test in patients receiving (○) methohexital, (△) etomidate, and (●) midazolam. Data are presented as mean values ± SEM; asterisks represent a significant difference from etomidate and methohexital groups ($P < 0.05$).

Table 5. Patient Recall of Perioperative Events in the Three Study Groups (%)

Event	Midazolam	Methohexital	Etomidate
Surgical incision	19	59*	52*
Intraop. events	0	36*	38*
Removal of drapes	10	41*	38*
Move to stretcher	20	63*	62*
Enter PACU	33	68*	90*
Discharge from PACU	100	100	100

*Significantly different from midazolam group, $P < 0.05$.

sedation while allowing for a rapid recovery from their CNS effects.

The continuous infusion technique we used rapidly achieved and maintained the desired degree of intraoperative sedation with methohexital, etomidate, and midazolam. Clinically, recovery from the sedative effects was prompt in all three groups after discontinuation of the sedative infusions. Despite the fact that the rate of midazolam clearance is slower than that of methohexital and etomidate (7–9), careful titration of midazolam allowed for an equally rapid recovery from its sedative effects (Fig. 3). On arrival in the PACU (within 10 minutes after discontinuation of the infusion), all patients readily responded to verbal stimulation, and less than 15% of the patients were considered to be clinically sedated (i.e., observer sedation score >2). Within 30 minutes, 77% of the patients were considered to be fully "awake and alert." This percentage increased to 86% and 99% at 60 and 90 minutes, respectively.

The digit–symbol substitution test, a cognitive function test that involves hand–eye coordination skills as well as recall of multiple pairings of digits and symbols, provided objective evidence for differences in the recovery rates for the three study medications. In the early postoperative period, performance was significantly poorer in patients given midazolam than in those given etomidate or methohexital. The rate of improvement in the performance scores with time was, however, similar for all three study medications (Fig. 5). Since there was no difference among the three study groups in the patient's subjective evaluation of the level of residual sedation, the differences in performance on the DSST may be a reflection of residual CNS effects of midazolam (10–12). Midazolam produced more profound amnesia for perioperative events than etomidate or methohexital (Table 5), and it is possible that residual amnesia contributed to the delayed recovery on the DSST in the midazolam group.

Although not evaluated in this study, our results are consistent with previous studies that suggested improved control of the clinical effects (e.g., sedation, analgesia), a decreased total drug requirement, and a more rapid recovery when continuous infusion techniques are used to administer sedative-analgesic medication (4,13). While MacKenzie and Grant reported a methohexital dosage requirement of 90 $\mu g \cdot kg^{-1} \cdot min^{-1}$ when administered by intermittent bolus injections for sedation during regional anesthesia (14), we reported an average methohexital requirement of 38 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for sedation when the same drug was administered as a variable-rate infusion. Using intermittent bolus injections of midazolam for sedation during regional anesthesia, Dixon et al. (12) reported a mean midazolam dose of 6.5 mg to achieve initial satisfactory sedation, in contrast to a mean loading dose of 3.7 mg in our study. In addition, 26% and 20% of their patients remained "moderately sedated to unresponsive-to-touch" at 1 and 2 hours, respectively, after surgery.

Compared to a previous investigation (15), administration of methohexital and etomidate by continuous infusion may have contributed to the lower incidence of pain on injection and myoclonus in our study (Table 4). However, one etomidate-treated patient developed prominent myoclonic activity before achieving an adequate level of sedation and was removed from the study. Although none of our patients required ventilatory assistance, episodes of arterial oxygen desaturation were reported during the maintenance infusion period. These episodes appeared to be due to partial airway obstruction associated with jaw relaxation and were readily reversed with verbal and/or gentle tactile stimulation of the patient. The use of pulse oximetry for monitoring oxygenation when intravenous sedation is used during regional anesthesia may prevent adverse sequelae related to unrecognized respiratory depression resulting from upper airway obstruction, skeletal muscle weakness, and/or depression of ventilatory drive (3). Side effects reported in the PACU were primarily related to the surgical procedure and regional anesthetic technique rather than to the sedative medication.

In summary, the continuous infusion of methohexital, etomidate, or midazolam produced a stable level of sedation during regional anesthesia and provided for a rapid recovery from the sedative effects of these centrally active drugs with minimal side effects. Although midazolam provided superior amnesia for perioperative events, postoperative recovery of cognitive function occurred more slowly with midazolam than either methohexital or etomidate. Nevertheless, PACU discharge times were similar for all three sedative treatment groups. Further controlled studies are required to determine if the infusion of intravenous sedative medication offers any clinical advantages over the traditional intermittent bolus administration technique during local and regional anesthesia. We conclude that the continuous infusion of rapid and short-acting sedative drugs can provide for a stable level of sedation during regional anesthesia that is associated with a rapid recovery of cognitive function and minimal side effects.

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Doxacurium Chloride for Neuromuscular Blockade before Tracheal Intubation and Surgery during Nitrous Oxide–Oxygen–Narcotic–Enflurane Anesthesia

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LENNON RL, HOSKING MP, HOUCK PC, ROSE SH, WEDEL DJ, GIBSON BE, ASCHER JA, RUDD GD. Doxacurium chloride for neuromuscular blockade before tracheal intubation and surgery during nitrous oxide–oxygen–narcotic–enflurane anesthesia. Anesth Analg 1989;68:255–60.

The neuromuscular effects of doxacurium (BW A938U) were studied in 36 patients, divided into four groups of 9 patients each, given doxacurium either 50 μg/kg (2 × ED_{95}) 5 or 4 minutes or 80 μg/kg (3 × ED_{95}) 4 or 3 minutes before tracheal intubation. Adequate neuromuscular relaxation permitted successful intubation at 5 minutes for doxacurium 50 μg/kg and at 4 minutes for 80 μg/kg. Time to 90% blockade was 5.4 ± 1.5 minutes for doxacurium 50 μg/kg and 3.5 ± 1.2 minutes for 80 μg/kg. Time to 25% spontaneous recovery was 84.7 ± 54.3 minutes for doxacurium 50 μg/kg and 164.4 ± 85.2 minutes for 80 μg/kg. Either neostigmine 45 μg/kg, neostigmine 60 μg/kg, or edrophonium 1000 μg/kg was given for reversal when T1 had spontaneously recovered to 25% of baseline level, T1 being the first response to repetitive train-of-four (TOF) stimuli (2 Hz for 2 seconds at 10-second intervals) expressed as percent of baseline level. The T4:T1 ratio is the amplitude of the fourth twitch relative to the first twitch in a TOF stimulus expressed as a ratio. T1 rapidly achieved 90% of baseline in 5–10 minutes after reversal of neuromuscular blockade. In contrast, the T4:T1 ratio lagged, recovering to a mean of 0.6 at 20 minutes when T1 was over 90% of baseline. Recovery patterns were not statistically significantly different (unpaired t-test) among the three reversal regimens. Therefore, the reversal data were pooled. No clinically significant hemodynamic effects occurred in any group. The authors conclude that doxacurium is a long-acting muscle relaxant that provides excellent intubating conditions within 5 minutes with 50 μg/kg and within 4 minutes with 80 μg/kg. Neuromuscular blockade lasts approximately 85 and 164 minutes, respectively. The neuromuscular blockade is pharmacologically readily reversible.

Key Words: NEUROMUSCULAR RELAXANTS—doxacurium.

Doxacurium chloride (BW A938U, Fig. 1) is a recently introduced long-acting neuromuscular blocking drug currently undergoing phase III clinical trials. Doxacurium is approximately two to three times as potent as pancuronium, with an ED_{95} of 23 μg/kg during balanced anesthesia (1). It is reported to be devoid of significant cardiovascular effects (2–7) and not to exhibit accumulation with supplemental doses (4,8). In addition, doxacurium has been reported to be readily reversible with standard clinical doses of anticholinesterase drugs (2).

At ED_{95} doses, doxacurium has a relatively slow onset to maximum blockade of 10–12 minutes (2). This study was performed, therefore, to determine if doxacurium could provide adequate conditions for tracheal intubation in a shorter period of time when administered in doses two to three times the ED_{95}. Further, we evaluated parameters of neuromuscular blockade, rate of spontaneous recovery, and efficacy of reversal.

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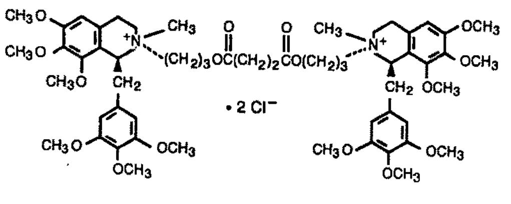

Doxacurium chloride (BW A938U)

Figure 1. Molecular structure of doxacurium (BW A938U) (molecular weight 1106.14).

Methods

Thirty-six ASA physical status 1 or 2 patients, 18–70 years of age, weighing 45–100 kg, scheduled for elective low to moderate risk surgical procedures were studied. Patients who were pregnant or had a history of malignant hyperthermia, drug abuse, or neuromuscular disorders or who had clinically significant psychiatric, cardiac, renal, or hepatic disease were excluded. Patients recently exposed to phenytoins, corticosteroids, antihistamines, tricyclic antidepressants, or antibiotics were also excluded. The study was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

Most patients were premedicated with 1–5 mg of midazolam in the operating room, where, after placement of an intravenous catheter, an automated sphymomanometer and ECG leads, one arm of the patient was secured to a padded armboard. A Grass FT 10 force displacement transducer was used to measure the adductor pollicis twitch responses, which were continuously recorded after induction of anesthesia on a Gould multichannel polygraph. General anesthesia was then induced with thiopental 4–7 mg/kg preceded, at the discretion of the investigator, by IV fentanyl 1.0–1.5 μg/kg. Additionally, most patients received 1–2 mg of midazolam in the operating room before induction of anesthesia. Upon loss of consciousness, nitrous oxide 60–70% and oxygen 40–30% were given by mask using a semiclosed system with additional fentanyl 0.5–1.5 μg/kg as needed to maintain hemodynamic stability and an adequate level of analgesia before intubation. Approximately 30 seconds following induction of general anesthesia, needle electrodes were placed near the ulnar nerve at the wrist. Supramaximal 0.2-millisecond square wave stimuli at a frequency of 2 Hz for 2 seconds in a train-of-four (TOF) pattern were delivered every 10 seconds by a Grass S88 stimulator continuously throughout the procedure. After establishment of a stable baseline twitch response, an intubating dose of doxacurium was injected over 5 seconds via a three-way stopcock inserted at the intravenous cannula. Immediately after the injection, the IV line was flushed by a rapid flow of IV fluid for 15 seconds. Patients in group A1 ($n = 9$) were given doxacurium 50 μg/kg and intubation was attempted in 5 minutes. Group A2 patients ($n = 9$) received doxacurium 50 μg/kg, and intubation was attempted in 4 minutes. Group B1 patients ($n = 9$) were given doxacurium 80 μg/kg, and intubation was attempted after 4 minutes. Group B2 patients ($n = 9$) received doxacurium 80 μg/kg, and intubation was attempted after 3 minutes. The same person formed all intubations. The intubationist was blinded to both time and dose of doxacurium.

Intubating conditions were rated grade 1–4:

1. Excellent: Easy passage of tube without coughing. Vocal cords relaxed.
2. Good: Passage of tube with slight coughing and/or bucking. Vocal cords relaxed.
3. Poor: Passage of the tube with moderate coughing and/or bucking. Vocal cords moderately adducted.
4. Not possible: Vocal cords tightly adducted.

Two patients were excluded from intubation analysis due to technical factors unrelated to neuromuscular blockade.

Following intubation, administration of nitrous oxide–oxygen–enflurane by endotracheal tube was initiated. A stable level of anesthesia was provided using enflurane (ET 0.8%), nitrous oxide–oxygen, and supplemental doses of fentanyl. End-tidal enflurane concentrations were continuously monitored by a Perkin-Elmer 1100 mass spectrometer. Body temperature was measured by esophageal temperature probe. If surgery was prolonged, additional doses of 5.0 μg/kg of doxacurium were administered when spontaneous recovery of T1 reached 25% of baseline levels.

Once the surgical procedure was concluded or when neuromuscular blockade was no longer required, pharmacologic reversal of residual doxacurium-induced block was initiated when spontaneous recovery of T1 reached 25% of baseline levels. Patients were randomized to receive either neostigmine 45 μg/kg, neostigmine 60 μg/kg, or edrophonium 1000 μg/kg in combination with atropine 15 μg/kg. Both T1 and the T4:T1 ratio were analyzed at the time of reversal and at 5-minute intervals for the next 20 minutes or until the nerve stimulator was discontinued. In 6 patients, neuromuscular blockade was still profound at the completion of surgery. Reversal of neuromuscular blockade was provided in the recovery room for these 6 patients, and these patients therefore were not included in the statistical analysis of recovery and reversal data. T1 is defined as the first

Table 1. Neuromuscular Function after Administration of Doxacurium

Neuromuscular parameter	50 μg/kg	80 μg/kg	*P*
Maximum block (%)	95.7 ± 5.2 (*n* = 18)	97.7 ± 1.2 (*n* = 18)	NS
Time to 90% block (min)	5.4 ± 1.5 (*n* = 17)	3.5 ± 1.2 (*n* = 17)	$P < 0.001$
Time to 10% recovery (min)	71.5 ± 49.3 (*n* = 14)	133.6 ± 67.1 (*n* = 13)	$P < 0.02$
Time to 25% recovery (min)	84.7 ± 54.3 (*n* = 12)	164.4 ± 85.2 (*n* = 9)	$P < 0.05$

Maximum block defined as percent depression below baseline levels of T, twitch response.
All values are mean ± SD. Differences between doses were analyzed with an unpaired *t*-test.

Table 2. Intubation Scores

Group	Intubating dose (μg/kg)	Time to intubation (min)	No. of patients given indicated intubating score				Mean intubation score (1–4)
			1	2	3	4	
A1	50	5	1	5	1	0	2.0 ± 0.6
A2	50	4	4	2	1	2	2.1 ± 1.3
B1	80	4	6	2	1	0	1.4 ± 0.7
B2	80	3	4	2	1	2	2.1 ± 1.3

There were no statistically significant differences between groups.
Intubation scores as described in text.

response to repetitive TOF stimuli expressed as a percent of baseline level. The T4:T1 ratio is defined as the amplitude of the fourth twitch relative to the first twitch in a TOF stimulus expressed as a ratio. All patients had physical examination 48 hours postoperatively and were followed until time of discharge from the hospital.

Differences between groups were analyzed with an unpaired *t*-test. Multiple comparisons within groups were analyzed by one-way ANOVA and a paired *t*-test with the Bonferroni adjustment. Nonparametric data were analyzed by the Kruskal–Wallis test. A randomization schedule was developed for reversal agents. Random numbers were generated using the procedure PLAN of SAS. All analyses were performed on an IBM XT PC using Stat Pac statistical analysis package. Data in tables and text are expressed as mean ± SD. Statistical significance was defined by $P < 0.05$.

Results

There were no significant differences in the mean age, height, or weight of patients between groups. Maximum block achieved was not significantly different between the two doses of doxacurium (Table 1). Time to 90% block in patients receiving doxacurium 50 μg/kg was 5.4 ± 1.5 minutes versus 3.5 ± 1.2 minutes for patients receiving 80 μg/kg ($P < 0.001$). For patients receiving 50 μg/kg, time to 10% and 25% spontaneous recovery was 71.5 ± 49.3 and 84.7 ± 54.3 minutes, respectively ($P < 0.002$). Time to 10% and 25% spontaneous recovery was significantly prolonged at 133.6 ± 67.1 ($P < 0.02$) and 164.4 ± 85.2 minutes, respectively, ($P < 0.05$), in patients receiving doxacurium 80 μg/kg.

Intubation scores are listed in Table 2. There were no failures to intubate at 5 minutes with doxacurium 50 μg/kg (group A1). When the intubating interval was decreased to 4 minutes (group A2), 2 of 9 patients could not be intubated due to inadequate muscle relaxation. Maintaining the intubating interval of 4 minutes but increasing the dose to 80 μg/kg once again resulted in no failures to intubate (group B1). Decreasing the intubating interval after 80 μg/kg from 4 to 3 minutes (group B2) resulted in two failures to intubate due to inadequate muscle relaxation. When analyzed by both χ^2 and Kruskal–Wallis tests for nonparametric data, there were no statistically significant differences between groups.

Reversal data are illustrated in Figures 2 and 3. Recovery of neuromuscular function after reversal of blockade was not significantly different between patients given doxacurium 50 or 80 μg/kg. Figures 2 and 3 show that T1 rapidly returned from 25% to 80% of control by 5 minutes and to 90% by 20 minutes. Similarly, the T4:T1 ratio recovered rapidly in the first 5 minutes after reversal but then plateaued so as not to exceed a mean value of 0.6 even at 20 minutes. No statistical differences in reversal characteristics existed between patients given neostigmine 45 μg/kg, neostigmine 60 μg/kg, or edrophonium when analyzed by one-way ANOVA. These data were therefore grouped.

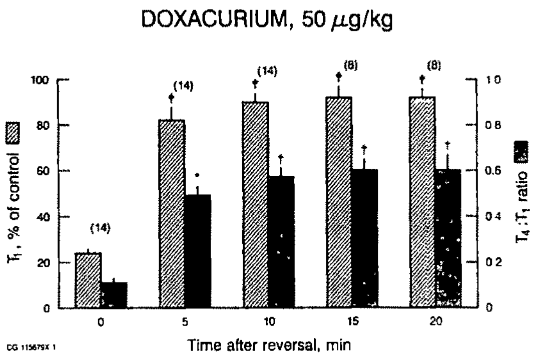

Figure 2. Pharmacologic reversal of doxacurium µg/kg with neostigmine 45 or 60 µg/kg or edrophonium 1000 µg/kg. Abscissa: Time in minutes after IV injection of antagonist. Left ordinate and diagonal striped bars: T1 expressed as percent of baseline. Right ordinate and shaded bars: T4:T1 ratio. (*n*): number of patients. Symbols indicate statistically significant differences from time zero. $* P < 0.002$; $† P < 0.001$; $‡ P < 0.0001$.

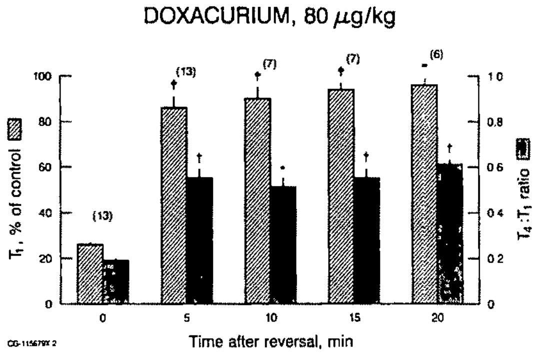

Figure 3. Pharmacologic reversal of doxacurium 80 µg/kg with neostigmine 45 or 60 µg/kg or edrophonium 1000 µg/kg. Abscissa: time in minutes after IV injection of antagonist. Left ordinate and diagonal striped bars: T1 expressed as percent of baseline. Right ordinate and shaded bars: T4:T1 ratio. (*n*): number of patients. Symbols indicate a statistically significant difference from time zero. $* P < 0.002$; $† P < 0.001$; $‡ P < 0.0001$.

There were no clinically significant changes in mean arterial pressure (MAP) or heart rate (HR) in any of the groups studied.

Discussion

This study confirms that doxacurium is an effective long-acting muscle relaxant without significant cardiovascular side effects in doses up to 3 × ED_{95} (7). Our data agree closely with recent reports that used a similar study design (8,9). An intubation dose of 50 µg/kg produces 90% blockade in approximately $5\frac{1}{2}$ minutes with a clinical duration of 85 minutes (time to 25% spontaneous recovery of T1). Increasing the intubating dose to 80 µg/kg decreases the onset time to 90% blockade to $3\frac{1}{2}$ minutes but doubles the clinical duration to 165 minutes. Decreased time of onset of blockade and prolonged time to spontaneous recovery with increasing doses are found with all nondepolarizing muscle relaxants (10).

Although blockade and recovery data for doxacurium have been thoroughly evaluated and reported in many studies, pharmacologic reversal of neuromuscular blockade after doxacurium has not been systematically analyzed or reported in adults. Sarner et al. found in children that pharmacologic reversal of doxacurium with neostigmine 60 µg/kg given when recovery of T1 was between 47 and 98% of baseline resulted in a T4:T1 ratio greater than 0.75 following within 0.16 to 5.7 minutes (11). In contrast, our study indicates a T4:T1 ratio greater than 0.75 after pharmacologic reversal is significantly delayed in adults. Figures 2 and 3 illustrate that if reversal is attempted when T1 has spontaneously recovered to 25% of baseline, then T1 rapidly approaches 90% of baseline within 5–10 minutes. However, the T4:T1 ratio lag, recovering only to a mean value of 0.6 even at 20 minutes, at which time T1 is 90% of baseline. Recovery of T1 and T4:T1 ratio after reversal is independent of the initial dose of doxacurium. This marked difference between our study and that of Sarner et al. could be accounted for by several variables: 1) Compared to adults, children have a tendency to require more doxacurium to achieve the same degree of neuromuscular blockade, and they tend to recover faster from the effect of the relaxant (12). 2) Sarner et al. used halothane as the anesthetic, whereas we used enflurane, which is known to potentiate muscle relaxants to a greater degree (13,14). 3) We reversed neuromuscular blockade in our patients when T1 was 25% of baseline while Sarner et al. did so when T1 was 47–98% of baseline. All of these factors could contribute to a more rapid return of a T4:T1 ratio greater than 0.75 in their study.

Although widely used as a method for monitoring recovery from neuromuscular blockade in both research and clinical applications, the mechanism for TOF fade, characterized by the increasingly diminished amplitude of the second, third, and fourth responses relative to the first response in a TOF stimulus, is currently unknown. A number of factors may influence the degree of fade, and various relaxants are associated with different effects on fade of TOF (15). During onset of block, the T4:T1 ratio bears no fixed relationship to the height of T1, while there is a constant and reliable relationship between the value of T1 and the T4:T1 ratio during offset (16). Graham et al. (17) found that twitch depression and T4:T1 ratio bear a fixed relation in time and, on the basis of a kinetic analysis model, concluded that different rate constants indicate separate sites of action. Bartkowski (18) demonstrated a plateau effect for reversal of neuromuscular blockade and recovery of the T4:T1 ratio. Because pharmacologic reversal is a process of indirect antagonism, the degree of recovery is limited by the amount of acetylcholine released and by the extent of alternative elimination pathways such as diffusion and reuptake, even when acetylcholine breakdown is maximally inhibited.

In light of these differences in response between T1 and the T4:T1 ratio following pharmacologic reversal of relaxants, separate pre- and postsynaptic receptor sites of action have been proposed. Single-twitch depression is generally considered to occur at classical postjunctional receptors, while fade may occur at prejunctional sites (19–21), ion channels (19,22,23), or other postjunctional sites (17,24,25). Regardless of the pre- or postsynaptic site of action, the pharmacologic reversal profile for doxacurium is consistent with those of other competitive neuromuscular blockers and also exhibits a ceiling effect for T4:T1 ratio recovery.

We evaluated intubating conditions by assigning an intubating score as described. However, there were no statistically significant differences between groups. The variability in intubating scores within groups reflect that adequate tracheal intubating conditions depend on depth of anesthesia, skill of the intubationist, and the degree of muscle relaxation. Our sample size was too small to control all these variables. The data indicate, however, that all patients could be intubated at 5 minutes with 50 μg/kg and at 4 minutes with 80 μg/kg doxacurium. At these doses and time, inadequate muscle relaxation never interfered with tracheal intubation.

Doxacurium had no clinically significant hemodynamic effects before intubation at doses several times the ED_{95}. Stoops et al. (5) reported no significant changes in MAP, HR, cardiac index, pulmonary capillary wedge pressure, or systemic vascular resistance in cardiac surgical patients associated with doxacurium. Two-dimensional transesophageal echocardiographic monitoring confirms the lack of effect of doxacurium on right and left ventricular performance (7).

In summary, doxacurium is a long-acting nondepolarizing neuromuscular blocking agent with no clinically significant effects on heart rate or mean arterial blood pressure in ASA physical status 1 and 2 patients. Tracheal intubation can be accomplished with adequate muscle relaxation 5 minutes after 50 μg/kg and 4 minutes after 80 μg/kg. However, this increase in intubating dose nearly doubled the clinical duration of blockade, from 85 to 165 minutes. T1 can be rapidly pharmacologically reversed to 90% of baseline in 5–10 minutes by neostigmine 45 or 60 μg/kg and edrophonium 1000 μg/kg, but the T4:T1 ratio does not exceed a mean value of 0.6 even 20 minutes after reversal even though T1 is 90% of baseline. The combination of hemodynamic stability and predictable neuromuscular blockade make doxacurium suitable for surgical cases of moderate to long duration.

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Influence of Nifedipine on Systemic and Regional Hemodynamics During Adenosine-Induced Hypotension in Dogs

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ROONEY MW, CRYSTAL GJ, SALEM MR, PAULISSIAN R. Influence of nifedipine on systemic and regional hemodynamics during adenosine-induced hypotension in dogs. Anesth Analg 1989;68:261–9.

Previous pharmacologic studies indicating competitive interactions between adenosine and nifedipine at the adenosine vascular receptor suggest that adenosine may be a less effective hypotensive drug after pretreatment with nifedipine. This hypothesis was tested in 18 pentobarbital-anesthetized, open-chest dogs by evaluating the hypotensive effects and regional hemodynamic responses to 60-minute intravenous adenosine infusions before and after bolus injection of nifedipine (20 μg/kg, IV). Regional blood flow was measured with 15-μm radioactive microspheres. Before nifedipine, infusion of adenosine at a rate of 126 ± 30 μmol/min caused a 50% reduction in mean aortic pressure that in the presence of no change in aortic blood flow was attributable to a proportional decrease in systemic vascular resistance. These systemic effects were associated with heterogeneous changes in regional blood flow; blood flow decreased in the renal cortex (−68%), pancreas (−50%), spleen (−77%), and skin (−61%); increased in the left (+112%) and right (+265%) ventricular myocardium; and did not change significantly in the duodenum, liver, skeletal muscle, or brain. Nifedipine did not alter the dose requirement or time course of the adenosine-induced hypotensive response or affect the associated systemic hemodynamic changes. Furthermore, nifedipine caused only minor alterations in the regional blood flow changes during adenosine-induced hypotension. Apparently the high plasma levels of adenosine required for controlled hypotension in the present study were sufficient to overcome the blocking influence of nifedipine at the adenosine vascular receptor. The study demonstrates that the hypotensive action of adenosine remains unimpaired after pretreatment with nifedipine. The present findings may have clinical relevance in patients with cardiovascular disease being treated with nifedipine who may need adenosine to lower blood pressure either to decrease bleeding or to decrease myocardial work and oxygen consumption.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—adenosine. PHARMACOLOGY, CALCIUM CHANNEL BLOCKERS—nifedipine.

Controlled hypotension is being used increasingly to minimize intraoperative blood loss and to provide a dry field to facilitate the surgery (1). The currently used hypotensive drugs (e.g., nitroprusside, nitroglycerin, and trimethaphan) have drawbacks including cyanide toxicity, tachyphylaxis, reflex tachycardia, and rebound hypertension (2–6). These drawbacks have stimulated efforts to identify and develop new hypotensive agents.

Among the most promising of the newly proposed hypotensive agents is adenosine. Adenosine, a metabolic breakdown product of adenosine triphosphate, is an endogenous vasodilator that has been implicated in local regulation of organ blood flow (7). Studies utilizing adenosine analogues have demonstrated that the vasodilating action of adenosine is mediated by a specific adenosine receptor on the outside of the vascular smooth muscle cell (7).

Intravenous infusion of adenosine both in dogs and in humans causes arterial hypotension that is rapidly achieved, easily controlled, and short-lived, with no hematologic or biochemical evidence of toxicity (2,8–12). Furthermore, adenosine-induced hypotension has a beneficial effect on myocardial oxygen

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The protocols used in this study were approved by the authors' institutional animal investigation committee.

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supply/demand balance by increasing coronary blood flow while at the same time decreasing cardiac work demand (9). Finally, because adenosine does not cross the blood-brain barrier it does not impair cerebral autoregulation of blood flow (10). This latter feature may be a distinct advantage during neurosurgery.

Nifedipine is a calcium channel antagonist that is widely prescribed for treatment of coronary vasospasm and angina pectoris as well as for a number of other diverse cardiovascular disorders (13). A number of recent reports have suggested that nifedipine may have complex and multiple interactions with adenosine (14–19). For example, nifedipine inhibits adenosine uptake from, and release into, the extracellular space, as well and also binds to adenosine vascular receptors. Furthermore, pretreatment with nifedipine attenuates significantly the vasodilator response during intracoronary infusion of adenosine in the intact canine heart. Such observations suggest that the hypotensive action of adenosine may be impaired in the presence of nifedipine. If so, this may be of clinical importance in patients with cardiovascular disease being treated with nifedipine who may need adenosine to lower blood pressure either to decrease bleeding or to decrease myocardial work and myocardial oxygen consumption.

An additional and increasingly frequent use of adenosine is as an agent to decrease myocardial work and oxygen consumption in patients with coronary artery disease. This use of adenosine can be seen both in anesthetized patients (especially during coronary bypass grafting) and in unanesthetized patients in coronary care units and intensive care units. This use of adenosine would have a relatively high likelihood of being associated with nifedipine treatment, which gives further clinical relevance to the question of whether nifedipine impairs the hypotensive actions of adenosine.

The study in anesthetized dogs reported here was designed to evaluate the hypotensive response and regional hemodynamic changes during intravenous infusion of adenosine in the absence and presence of nifedipine.

Methods

Experimental Preparation

Experiments were performed on 18 mongrel, heartworm-free, conditioned dogs of either sex (weight range 21–24 kg). Anesthesia was induced with pentobarbital sodium, 30 mg/kg, with a maintenance dose of 2 $mg \cdot kg^{-1} \cdot hr^{-1}$ to achieve a stable anesthetic state. After tracheal intubation, the animals were ventilated by a Harvard respiratory pump with room air. Physiological levels of arterial Po_2 and Pco_2 were established initially by adjusting the volume and rate of the respirator and by adding oxygen to the inspired gas. The respirator settings were not changed during the course of an experiment. Sodium bicarbonate solution was administered as necessary during recovery periods to correct hypotension-induced metabolic acidosis. Arterial blood gas tensions and pH were measured electrometrically (Instrumentation Laboratory, Model 1306). Rectal temperature was monitored and maintained at 38°C with a heating pad.

Polyethylene cannulas were inserted 1) into the thoracic aorta via the right femoral and right brachial arteries for monitoring aortic blood pressure and for obtaining samples of arterial blood for measurement of gas tensions and 2) into the right femoral vein for administration of supplementary anesthetic and other intravenous injections. The heart was exposed through a left thoracotomy in the fourth intercostal space, and additional polyethylene cannulas were placed in 1) the left atrium via the atrial appendage for monitoring left atrial pressure and for injecting radioactive microspheres and 2) the left ventricle via the left atrial appendage and the mitral valve for measuring left ventricular pressure. A noncannulating flow transducer was placed around the ascending aorta to measure cardiac output (less coronary blood flow) using an electromagnetic flowmeter (Narco Biosystems). In 4 dogs another flow transducer was placed around the circumflex or left anterior descending coronary artery so that coronary blood flow could be monitored continuously. Anticoagulation was achieved with intravenous injections of heparin (300 U/kg). Pancuronium (0.15 mg/kg) was administered to facilitate controlled ventilation.

Blood pressures were measured with Statham transducers (Model P23ID) and averaged electronically. The left ventricular systolic pressure pulse was used to drive a cardiotachometer and a differentiator to yield $(dP/dt)_{max}$. Blood pressures, electromagnetic blood flows, and heart rate were recorded with a Gould recorder (Model 2800S). Systemic vascular resistance (excluding the coronary bed) was computed by dividing mean aortic pressure by mean aortic blood flow.

The statistical significance of differences between treatment means was tested using a randomized block analysis of variance in conjunction with the Student–Newman–Keuls test (20). A value of $P <$ 0.05 was considered statistically significant.

Measurement of Regional Blood Flow

Regional blood flow was measured with 15 ± 3-μm microspheres labeled with γ-emitting radionuclides ^{141}Ce, ^{46}Sc, ^{85}Sr, and ^{113}Sn (New England Nuclear Corp.; 3M Company) (21). Before injection, microspheres were dispersed in a solution of 10% dextran and agitated in a vortex mixer and in an ultrasonic bath. Approximately 1×10^6 microspheres were administered for each flow determination. The microspheres were flushed into the left atrium over 30 seconds with 5 ml of body-temperature isotonic saline. Administration of microspheres had no detectable effect on monitored hemodynamic parameters. Beginning simultaneously with each microsphere injection, duplicate reference arterial samples were collected for 3 minutes through two cannulas of different lengths inserted into the aorta via the left femoral artery. Similar radioactivities of these duplicate reference samples verified adequate mixing of microspheres in the left ventricular output.

After the final injection of microspheres, the heart was stopped by intravenous injection of KCl, excised, and trimmed of adipose tissue, valves, and great vessels. Transmural myocardial samples were obtained from the left and right ventricular free walls. The brain was removed, and samples were obtained from the cerebral cortex, cerebellum, pons, medulla, and cervical spinal cord. Samples were also obtained from the renal cortex, pancreas, spleen, liver, duodenum, skin, and skeletal muscle. Most tissue samples contained at least 400 microspheres to ensure high-precision, low-error flow estimates (22). The precision of measurements in tissues with low flows (for example, skin) was improved by using larger samples. Each sample was transferred to a tared counting tube. The tissue and reference blood samples were weighed and analyzed for radioactivity with a gamma scintillation counter equipped with a multichannel analyzer (LKB Model 1282-002). Isotope separation was accomplished by standard techniques of gamma spectroscopy. Values for regional blood flow (RBF) in milliliters per minute per 100 g were calculated from the equation

$$\mathrm{RBF} = \mathrm{ABF} \times (\mathrm{MC}/\mathrm{AC}) \times 100$$

where ABF is the arterial reference sampling (ml/min), MC is microsphere radioactivity (counts$\cdot$min$^{-1}\cdot$g^{-1}) in the tissue samples, and AC is the total microsphere radioactivity (counts/min) in the arterial reference samples.

Radioactivity in liver reflected hepatic artery blood flow but not portal vein blood flow, since 15-μm microspheres are trapped completely in the mesenteric and splenic circulations (23).

Experimental Protocols

Series 1. Adenosine-induced hypotension before and after nifedipine treatment. In 9 dogs, adenosine-induced hypotension was induced before and after treatment with the calcium channel blocker nifedipine. The dogs were permitted to stabilize for at least 30 minutes after surgical preparation before baseline systemic measurements were obtained and the first microspheres were injected. Hypotension was then produced in the absence of nifedipine by infusing adenosine (60 mmol/L in isotonic saline) intravenously at a rate sufficient to reduce mean aortic blood pressure by 50% (126 ± 30 μmol/min). The rate of infusion of adenosine was held constant throughout the hypotensive period. Because a highly concentrated adenosine solution was used, infusion rates of solution (2.1 ± 0.5 ml/min) needed to achieve significant hypotension were low. This precluded decreases in hematocrit during the extended period of controlled hypotension. Since adenosine is relatively insoluble in water, the adenosine solution required continuous heating and stirring to avoid precipitation of adenosine crystals. After 60 minutes of adenosine-induced controlled hypotension, systemic hemodynamic measurements were made and a second set of microspheres were injected.

Adenosine infusion was discontinued after the second injection of microspheres, and a 60-minute recovery period followed. Due to the limited number of differently labeled microspheres available (four), regional blood flow was not measured during the recovery period; however, it was assumed that since hemodynamic functions such as arterial blood pressure and heart rate had returned to baseline level this was also the case for tissue blood flows. Following apparent recovery from the initial adenosine infusion, nifedipine (20 μg/kg) was injected intravenously over 5 minutes. Nifedipine (Procardia; Pfizer Pharmaceutical) was dissolved in a solution containing 15% ethylene glycol, 15% ethyl alcohol, and 70% isotonic saline and was protected from light to prevent photodegradation (24). Nifedipine injection caused an immediate increase in coronary blood flow measured electromagnetically accompanied by arterial hypotension. Both these effects subsided within 15–30 minutes. At this time, the third set of microspheres were injected, and measurements of systemic hemodynamic parameters were obtained to characterize steady-state conditions in the presence of nifedipine

Table 1. Systemic Hemodynamic Changes during Adenosine-induced Hypotension before and after Nifedipine (NIF)

	Control	Adenosine	Recovery	Post-NIF baseline	Adenosine
MAP	98 ± 4	47 ± 2*	98 ± 4	94 ± 5	46 ± 4*
MLAP	4 ± 1	5 ± 2	4 ± 2	3 ± 1	4 ± 1
$(dP/dt)_{max}$	1019 ± 72	727 ± 92*	1008 ± 95	1150 ± 173	733 ± 133*
HR	169 ± 9	107 ± 10*	164 ± 7	161 ± 7	99 ± 88*
MAF	923 ± 81	864 ± 84	880 ± 91	850 ± 72	861 ± 67
SVR	0.117 ± 0.010	0.059 ± 0.004*	0.132 ± 0.012	0.134 ± 0.011	0.055 ± 0.003*
Arterial values					
pH	7.38 ± 0.01	7.24 ± 0.02*	7.35 ± 0.02	7.36 ± 0.02	7.23 ± 0.03*
P_{CO_2}	30 ± 2	32 ± 3	39 ± 3	38 ± 3	34 ± 3
P_{O_2}	124 ± 13	130 ± 11	115 ± 8	110 ± 10	121 ± 12
HCT	43 ± 1	41 ± 1	42 ± 2	42 ± 2	40 ± 2

Values are mean ± SE in 9 dogs.

$^*P < 0.05$, from preadenosine value.

Abbreviations: MAP, mean aortic pressure (mm Hg); MLAP, mean left atrial pressure (mm Hg); $(dP/dt)_{max}$, left ventricular $(dP/dt)_{max}$ (mm Hg/sec); HR, heart rate (beats/min); MAF, mean aortic flow excluding coronary bed (ml/min); SVR, systemic vascular resistance excluding coronary bed (mm $Hg \cdot ml^{-1} \cdot min^{-1}$); P_{O_2}, oxygen tension (mm Hg); P_{CO_2}, carbon dioxide tension (mm Hg); HCT, hematocrit (%)).

just before the second adenosine infusion. Then adenosine was infused at the same rate as that used in the absence of nifedipine and, after 60 minutes of hypotension, final systemic hemodynamic measurements were made and a fourth set of microspheres were injected.

Series 2. Adenosine-induced hypotension with recovery flow values. The finding in series 1 of significant steady-state reductions in renal cortical and splenic blood flows after nifedipine administration (Table 2) was inconsistent with previous reports indicating minor effects (25). This suggested that these regional vasoconstrictor responses may have been residual effects of the preceding adenosine infusion. To examine this possibility, hemodynamic responses were evaluated in 4 dogs under control conditions, after 60 minutes of adenosine-induced hypotension, and after 60 minutes of recovery from hypotension. After recovery, a second infusion of adenosine was performed at the same rate as the initial infusion in order to evaluate possible tachyphylaxis to repeated administrations of adenosine.

Series 3. Adenosine-induced hypotension only after nifedipine. Series 2 revealed a significant residual regional vasoconstrictor effect after adenosine infusion (Table 4) that confounded interpretation of results after nifedipine in series 1. To avoid this problem, another series of studies was conducted (series 3) in 5 dogs in which hemodynamic effects of nifedipine alone and of adenosine-induced hypotension following nifedipine were evaluated without prior adenosine-induced hypotension. After stabilization of the animal preparation, measurements of regional and systemic hemodynamic parameters were initially obtained under control conditions. Nifedipine (20 μg/kg) was then administered as described above, and these measurements were repeated. Adenosine was then infused at a rate sufficient to reduce mean arterial blood pressure by 50%. Microspheres were then injected and systemic hemodynamic measurements were made after 60 minutes of adenosine-induced hypotension and after 60 minutes of recovery.

Results

Adenosine-Induced Hypotension without Nifedipine

Adenosine infusion promptly reduced aortic pressure. The hypotension was stable and easily controlled with no evidence of tachyphylaxis. Systemic effects of adenosine-induced hypotension without nifedipine are summarized in Tables 1 and 3. Adenosine-induced hypotension was accompanied by decreases in left ventricular $(dP/dt)_{max}$, heart rate, and systemic vascular resistance, without changes in mean left atrial pressure or mean aortic blood flow. Arterial blood gas tensions were also not changed, although pH decreased modestly. Hemodynamic parameters returned to baseline rapidly (within 5 minutes) after discontinuation of adenosine infusion. When a second identical intravenous infusion of adenosine was carried out in the same dog, systemic hemodynamic effects were similar to those during the initial infusion (Table 3).

Regional vascular effects of adenosine-induced hypotension without nifedipine are presented in Tables 2 and 4. Adenosine-induced hypotension reduced blood flow in the renal cortex, pancreas, spleen, and skin and increased blood flow in the myocardium but

Table 2. Changes in Regional Blood Flow [ml·min^{-1}·(100 g)$^{-1}$] during Adenosine-Induced Hypotension before and after Nifedipine (NIF)

	Control	Adenosine	Post-NIF baseline	Adenosine
Renal cortex	518 ± 36	166 ± 26*	317 ± 62*	131 ± 30*
Pancreas	14 ± 2	7 ± 1*	14 ± 1	13 ± 2
Duodenum	27 ± 4	25 ± 4	31 ± 4	37 ± 5
Liver (hep. bed)	20 ± 2	15 ± 4	19 ± 4	14 ± 3
Spleen	142 ± 28	33 ± 8*	40 ± 8*	31 ± 7*
Skeleton muscle	3.6 ± 0.5	3.4 ± 0.7	4.7 ± 0.9	3.2 ± 0.7
Skin	3.3 ± 0.3	1.3 ± 0.2*	3.3 ± 0.8	1.7 ± 0.4*
Brain				
cerebral cortex	37 ± 2	39 ± 4	36 ± 3	33 ± 4
cerebellum	32 ± 2	33 ± 4	30 ± 2	30 ± 4
pons	23 ± 3	23 ± 2	24 ± 2	24 ± 2
medulla	25 ± 2	27 ± 1	26 ± 2	27 ± 1
spinal cord	14 ± 2	16 ± 1	16 ± 3	16 ± 2
Myocardium				
left ventricle	84 ± 5	178 ± 16*	130 ± 9*	163 ± 8*
right ventricle	52 ± 6	190 ± 20*	104 ± 8*	130 ± 6*

Values are mean ± SE in 9 dogs.
*$P < 0.05$, from control.

Table 3. Systemic Hemodynamic Changes during Sequential Identical Hypotensive Infusions of Adenosine

	Control I	Adenosine I	Control II (recovery)	Adenosine II
MAP	104 ± 9	51 ± 4*	108 ± 10	51 ± 4*
MLAP	3 ± 1	4 ± 1	4 ± 1	5 ± 1
$(dP/dt)_{max}$	1025 ± 37	669 ± 74*	981 ± 46	581 ± 87*
HR	186 ± 16	110 ± 12*	187 ± 13	110 ± 14*
MAF	1116 ± 92	1018 ± 104	1015 ± 41	1087 ± 63
SVR	0.094 ± 0.009	0.052 ± 0.007*	0.107 ± 0.009	0.048 ± 0.005*
Arterial values				
pH	7.37 ± 0.01	7.30 ± 0.02*	7.37 ± 0.01	7.25 ± 0.03*
Pco_2	35 ± 2	35 ± 2	35 ± 1	37 ± 1
Po_2	133 ± 18	111 ± 15	114 ± 20	114 ± 18
HCT	43 ± 1	41 ± 1	42 ± 1	42 ± 1

Values are mean ± SE in 4 dogs. Abbreviations and units are the same as shown on Table 1.
*$P < 0.05$, from control I.

did not affect blood flow in the duodenum, liver, skeletal muscle, or brain. Despite the return of systemic hemodynamic parameters to baseline after adenosine infusion, blood flow remain reduced in the renal cortex and spleen (Table 4).

Adenosine-Induced Hypotension with Nifedipine

Nifedipine itself caused no systemic hemodynamic changes (Tables 1 and 5) or changes in regional blood flow (Table 6). Nifedipine did not alter the rate of adenosine infusion required to reduce mean aortic pressure by 50% or the time course of the hypotensive response. Also, nifedipine did not alter the systemic hemodynamic responses associated with adenosine-induced hypotension. Regionally, nifedipine prevented the reduction in blood flow in the pancreas and spleen during adenosine-induced hypotension, but it had no effect on blood flow responses in other organs.

Discussion

The findings during adenosine-induced hypotension in the absence of nifedipine confirm previous reports from this laboratory and others (2,8–12). Intravenous adenosine caused aortic hypotension that was rapid in onset, easily controlled, and spontaneously and readily reversible when discontinued. There was no need to augment the dose requirement of adenosine

Table 4. Changes in Regional Blood Flow [ml·min^{-1}·(100 g)$^{-1}$) during Sequential Identical Hypotensive Infusions of Adenosine

	Control I	Adenosine I	Control II (recovery)	Adenosine II
Renal cortex	545 ± 53	162 ± 7*	336 ± 45*	194 ± 12*
Pancreas	26 ± 5	10 ± 1*	20 ± 3	10 ± 1*
Duodenum	26 ± 5	25 ± 3	28 ± 7	27 ± 6
Liver (hep. bed)	16 ± 3	17 ± 2	18 ± 3	16 ± 2
Spleen	143 ± 28	35 ± 4*	51 ± 7*	32 ± 3*
Skeletal muscle	3.8 ± 0.4	3.7 ± 0.3	3.4 ± 0.3	4.0 ± 0.3
Skin	3.0 ± 0.2	1.5 ± 0.2*	3.0 ± 0.3	1.3 ± 0.1*
Brain				
cerebral cortex	38 ± 2	38 ± 2	36 ± 3	38 ± 3
cerebellum	33 ± 2	34 ± 1	33 ± 1	34 ± 2
pons	21 ± 1	26 ± 1	22 ± 2	25 ± 2
medulla	28 ± 3	30 ± 1	24 ± 3	32 ± 4
spinal cord	15 ± 1	15 ± 1	13 ± 1	15 ± 1
Myocardium				
left ventricle	87 ± 5	207 ± 30*	91 ± 11	202 ± 25*
right ventricle	68 ± 4	167 ± 30*	72 ± 12	172 ± 21*

Values are mean ± SE in 4 dogs.
*$P < 0.05$, from control I.

Table 5. Systemic Hemodynamic Changes during Adenosine-Induced Hypotension after Administration of Nifedipine (NIF)

	Control	Post-NIF baseline	Adenosine	Recovery
MAP	106 ± 7	99 ± 5	50 ± 4*	92 ± 6
MLAP	4 ± 1	4 ± 1	4 ± 1	4 ± 2
(dP/dt)$_{max}$	1130 ± 89	1160 ± 53	840 ± 51*	1240 ± 104
HR	181 ± 11	187 ± 13	131 ± 17	179 ± 11
MAF	990 ± 76	923 ± 53	885 ± 87	960 ± 49
SVR	0.123 ± 0.012	0.124 ± 0.016	0.061 ± 0.013*	0.101 ± 0.019
Arterial values				
pH	7.40 ± 0.01	7.36 ± 0.01	7.24 ± 0.03*	7.39 ± 0.01
Pco$_2$	36 ± 2	37 ± 2	41 ± 2	39 ± 2
Po$_2$	135 ± 30	101 ± 10	98 ± 9	121 ± 26
HCT	41 ± 1	42 ± 1	41 ± 3	41 ± 2

Values are mean ± SE in 5 dogs.
*$P < 0.05$, from control. Abbreviations and units same as shown on Table 1.

once the desired level of aortic pressure was achieved and no blunting of hypotension during a second identical infusion of adenosine in the same dog. These observations are in keeping with previous reports that circulatory tachyphylaxis to effects of adenosine does not develop (8,9,26). There was no evidence of drug toxicity during adenosine infusion. Cardiac function was well maintained during adenosine infusion, and systemic hemodynamic parameters recovered promptly when the infusion was discontinued. Although a modest reduction in arterial pH was observed, this was likely a reflection of mild metabolic acidosis due to reduced perfusion of peripheral tissue and not directly attributable to adenosine per se.

Adenosine-induced hypotension was caused by a decrease in systemic vascular resistance. Although adenosine did decrease heart rate, stroke volume apparently increased sufficiently to maintain cardiac output. Since adenosine is free of positive inotropic effects (26), the increase in stroke volume was probably due to decreased left ventricular afterload in the presence of preserved preload (11). The bradycardia was probably due to direct suppression of pacemaker activity in the sinoatrial node by adenosine (27) sufficient to override the baroreceptor-mediated increase in heart rate associated with aortic hypotension (28). Such reflex tachycardia is frequently encountered when other drugs are used to produce controlled hypotension (1).

Table 6. Changes in Regional Blood Flow [ml·min^{-1}·(100 g)$^{-1}$] during Adenosine-Induced Hypotension after Nifedipine (NIF)

	Control	Post-NIF baseline	Adenosine	Recovery
Renal cortex	590 ± 61	531 ± 58	268 ± 41*	288 ± 76*
Pancreas	14 ± 1	13 ± 2	11 ± 5	13 ± 2
Duodenum	35 ± 6	32 ± 7	37 ± 6	24 ± 4
Liver (hep. bed)	21 ± 7	28 ± 5	28 ± 5	20 ± 6
Spleen	142 ± 31	125 ± 29	90 ± 10	127 ± 37
Skeletal muscle	4.0 ± 0.8	5.9 ± 1.5	3.7 ± 1.2	4.3 ± 0.8
Skin	2.3 ± 0.3	1.7 ± 0.2	1.3 ± 0.2*	2.0 ± 0.3
Brain				
cerebral cortex	37 ± 3	31 ± 4	39 ± 2	33 ± 5
cerebellum	34 ± 2	29 ± 5	33 ± 1	36 ± 3
pons	22 ± 1	22 ± 4	23 ± 1	25 ± 3
medulla	30 ± 1	27 ± 5	23 ± 1	25 ± 3
spinal cord	14 ± 2	12 ± 1	13 ± 1	16 ± 2
Myocardium				
left ventricle	79 ± 9	94 ± 20	197 ± 42*	96 ± 13
right ventricle	59 ± 6	77 ± 16	163 ± 26*	78 ± 13

Values are mean ± SE in 5 dogs.
*$P < 0.05$, from control.

Local intraarterial infusion of adenosine causes vasodilation in most vascular beds (29–31) via interaction with an adenosine receptor located on the outside of the vascular smooth muscle cell (7). This direct mode of action contrasts with that of adenosine triphosphate, another purported hypotensive agent, the vasodilator capability of which depends upon an intermediate substance released from the vascular endothelium, a so-called endothelium-derived releasing factor (EDRF) (32,33).

Despite a direct vasodilating effect of adenosine, flow in several tissues, namely the pancreas, spleen, and skin, decreased during intravenous adenosine infusion. This suggests that the direct vascular effect of adenosine in these tissues was antagonized by a generalized vasoconstrictor mechanism, probably the sympathetic vasoconstrictor nerves as part of the baroreceptor reflex response to aortic hypotension (28). Because the aforementioned tissues subserve noncritical functions with relatively modest oxidative requirements, reduced perfusion during the limited duration of controlled hypotension should be well tolerated and pose no systemic risk.

Adenosine has a paradoxical vasoconstrictor effect in the renal circulation (34). This vasoconstrictor effect of adenosine in the present study was demonstrated by pronounced decreases in renal cortical blood flow that were far in excess of those expected from decreases in driving pressure alone. The magnitude of the reduction in renal cortical blood flow (−68%) warrants concern, especially in patients with preexisting renal disease.

The persistent vasoconstriction in the renal cortex and spleen after complete recovery from adenosine-induced hypotension is noteworthy. The mechanism for this effect remains uncertain. Since adenosine itself is rapidly inactivated in the body tissues, it was presumably not directly responsible for this localized vasoconstriction. Previous reports of stable arterial plasma concentrations of renin and norepinephrine during adenosine-induced hypotension in anesthetized dogs suggest that these factors also were not involved (11).

Adenosine-induced hypotension influenced favorably global left ventricular oxygen supply/demand balance because it increased the oxygen supply (myocardial blood flow) while reducing parameters of oxygen demand such as heart rate and left ventricular afterload (35). The direct vasodilating action of adenosine no doubt was the major factor in the increase in myocardial blood flow. However, another factor contributing to augmented left ventricular perfusion was attenuation of the systolic extravascular component of coronary vascular resistance because of bradycardia and reduced intramyocardial pressure secondary to reduced intracavitary pressure (36).

In dogs with chronic coronary occlusions, intracoronary administrations of adenosine cause a maldistribution of left ventricular perfusion resulting in ischemia in collateral-dependent myocardium, the so-called coronary steal phenomenon (37). Although a concurrent reduction in myocardial oxygen demands should have an ameliorating influence on the development of myocardial ischemia during adenosine-induced hypotension, the use of adenosine as hypotensive agent in patients with significant coronary artery disease would appear contraindicated.

Intravascular adenosine cannot affect cerebral vascular smooth muscle directly because it does not cross the blood-brain barrier (10). Thus the preserved cerebral perfusion during adenosine-induced hypotension reflected strictly the well-developed tendency for pressure-flow autoregulation in the brain (38).

Nifedipine is a calcium antagonist with a wide spectrum of therapeutic effects. Although other calcium antagonists, including verapamil and diltiazem, are also widely prescribed, they have different modes of action and would not be expected to influence the hypotensive effects of adenosine (13). The 20-μg/kg intravenous dose of nifedipine was selected for two reasons. First, it was demonstrated to yield plasma levels in the therapeutic range in humans (24). Second, it was shown to block completely the significant vasodilating effects of intracoronary infusions of adenosine (15).

A reasonable question is whether plasma levels of nifedipine remained elevated during the 60-minute hypotensive period. Although measurements of plasma nifedipine were not obtained in this study, previous estimates of plasma half-life [range 1–5 hours (24,39)] suggest that nifedipine levels remained appreciable and within the therapeutic range.

Previous studies examining effects of nifedipine on systemic and regional hemodynamics have been summarized by Flaim and Kanda (25). These studies showed wide variation in species, experimental model, and route, dose, and protocol for nifedipine administration, all of which complicate relating the results of earlier studies to those obtained in the present study. However, it is worth noting that other studies that examined hemodynamic responses after comparable intravenous bolus injections of nifedipine in pentobarbital-anesthetized dogs also found initially pronounced reductions in aortic pressure and increases in coronary blood flow that returned to baseline within 20–30 minutes (15).

Despite previous evidence that nifedipine may inhibit the local vasodilating effects during intracoronary infusion of adenosine (15), nifedipine did not blunt systemic hypotension or coronary hyperemia during intravenous infusions of adenosine in this study. This is likely related to plasma adenosine concentrations during induced hypotension that were at least 20–30 times those evaluated during the intracoronary infusions (40). If, as has been speculated, a competitive pharmacologic interaction exists between adenosine and nifedipine at an adenosine vascular receptor (15), it is conceivable that the very high plasma adenosine concentrations evident in this study overcame the nifedipine blockade.

The tendency for nifedipine to blunt vasoconstrictor responses in splanchnic beds, that is, pancreas and spleen, during adenosine-induced hypotension likely reflects the ability of nifedipine to inhibit the sympathetic control of vasomotor tone during activation of the baroreceptor reflex pathway (25).

In conclusion, this study demonstrates that adenosine remains an effective, safe, and practical hypotensive agent in the presence of nifedipine. Our findings may have clinical importance in patients with cardiovascular disease being treated with nifedipine who may need adenosine to lower blood pressure either to decrease bleeding or to decrease myocardial work and oxygen consumption.

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Anesthesia for Cesarean Section—Effects on Neonates

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ONG BY, COHEN MM, PALAHNIUK RJ. Anesthesia for cesarean section—effects on neonates. Anesth Analg 1989;68:270–5.

The effects of general and regional anesthesia on neonates after cesarean section have been studied mainly on elective cases. In this paper we studied infants delivered by elective and nonelective cesarean section at the Winnipeg Women's Hospital from 1975 to 1983 (n = 3940) to determine the effect of anesthetic technique on neonatal outcomes. A trained anesthesia nurse interviewed all parturients and reviewed their antepartum, labor and delivery, and anesthesia records. Assessments of neonatal outcomes were based on 1- and 5-minute Apgar scores, need for positive pressure oxygen by mask or intubation, and neonatal deaths (within 30 days). These outcomes were determined in three subgroups of neonates delivered by cesarean section: those delivered by elective section, those delivered by urgent cesarean section for dystocia or failure of labor to progress, and those delivered by section because of fetal distress. Overall, 12.5% of the infants had 1-minute Apgar scores of 4 or less, and 1.4% had 5-minute Apgar scores of 4 or less. Neonates born to mothers given general anesthesia had worse outcomes than those born to mothers given regional anesthesia. Among neonates delivered after elective section, general anesthesia was associated with a higher incidence of low Apgar scores at 1 minute. In neonates delivered by nonelective section, general anesthesia was associated with higher rates of low Apgar scores at 1 and 5 minutes as well as greater requirements for intubation and artificial ventilation. There were no differences seen in neonatal death rates with general and regional anesthesia in the three groups. Using a multivariate analysis to control for differences among neonates with regard to maternal age, parity, presence of antepartum disease, labor complications, presence of fetal distress, gestational age, multiple birth, use of narcotics or sedatives during labor, elective versus nonelective section, and year of birth, the risk of poor neonatal outcome remained greater after general anesthesia than after regional anesthesia. We conclude that infants delivered by cesarean section under general anesthesia are more likely to be depressed and more likely to require active resuscitation than those delivered by cesarean section with regional anesthesia. However, with appropriate neonatal care, the choice of anesthetic technique does not appear to affect neonatal survival in the short term.

Key Words: ANESTHESIA—obstetric.

The influences of general and regional anesthesia on neonates after cesarean section deliveries have been studied mainly after elective procedures. Some of these studies (1–4) did not demonstrate any significant difference in Apgar scores between infants whose mothers received general anesthesia and infants whose mothers received regional anesthesia. Other studies (5–8) found that neonates of mothers who had regional anesthesia were in better clinical condition after elective cesarean section. Many of these studies were done with small numbers of selected parturients and may not be widely applicable to a general obstetric population. Marx et al. (9) examined 126 neonates who had fetal distress necessitating emergency cesarean section delivery and found that neonates of mothers who had regional anesthesia had better Apgar scores. To determine the influence of anesthetic technique on neonatal condition among all infants delivered by cesarean section, especially those for nonelective indications, we examined the outcomes of neonates delivered by cesarean section at the Winnipeg Women's Hospital from 1975 to 1983.

Methods

The data are derived from an obstetric anesthesia follow-up program at the Winnipeg Women's Hospi-

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tal from 1975 to 1983. A full description of the patient population and study methods has been published previously (10). This hospital serves as one of two tertiary referral hospitals for a population of about 1.5 million and also functions as a community hospital for women in the adjacent neighborhoods. The Department of Anesthesia provides 24-hour coverage with a staff and a resident anesthesiologist on duty in the hospital at all times. A resident in neonatology, a neonatology nurse, and/or a neonatalogist attend the nonelective cesarean section deliveries to aid in management of the infants.

For the anesthesia follow-up study, a specially trained anesthesia nurse (the same person throughout the 9-year period) reviewed the hospital charts for all parturients and also interviewed those who received an anesthetic. Thus all those having a cesarean section were interviewed. The review included the antepartum, labor and delivery, and anesthesia records. The variables recorded by the nurse included information on antepartum conditions, factors complicating labor and delivery, and the infants' Apgar scores. The Apgar scores were generally determined by the neonatology staff caring for the neonate. The final data base included information on 22,925 infants, representing 71% of all infants delivered by whatever means at the Winnipeg Women's Hospital in the 9-year period. Those cases not included were mainly delivered while the follow-up nurse was not on duty during holidays and some weekends. A small number of cases (1.5%) were excluded due to coding or transcription errors. From this data base we selected all infants delivered by cesarean section (n = 3940).

At our hospital, the majority of regional anesthetics were in the form of epidural anesthesia, with 1% being spinal anesthetics. The general anesthesia technique commonly employed during the study period was as follows: The parturients were given 100% oxygen by face mask and a small dose of nondepolarizing muscle relaxant while the surgical preparations were in progress. Left uterine displacement was maintained with a wedge under the right hip. Application of cricoid pressure, rapid sequence intravenous induction with thiopental (4 mg/kg) and succinylcholine (1.5 mg/kg), and tracheal intubation were performed immediately before skin incision. Anesthesia was maintained with 50% nitrous oxide, 50% oxygen, and small amounts of potent inhalational anesthetic (e.g., 0.5% halothane) until delivery of the infant and clamping of the cord. Narcotic supplement and higher nitrous oxide concentrations were then used for the remainder of the procedure. Ketamine 1 mg/kg was usually used instead of thiopental when maternal hypovolemia was suspected. The induction–delivery interval was 10 minutes or less for 98.8% of the anesthetics in which such time intervals were recorded; 97.5% of the uterine incision–delivery intervals were 120 seconds or less.

We were interested in determining whether the choice of regional or general anesthetic technique for cesarean section affected the neonatal outcomes. The neonatal outcomes used for our assessment included 1- and 5-minute Apgar scores, need for oxygen by mask or intubation, and neonatal deaths. Neonatal deaths (within 30 days of delivery) were determined independently as part of a study of genetic abnormalities.

Since the choice of anesthetic technique might be affected by the indications for the section, the data were analyzed in two ways to control for this confounding factor. The first analysis was done by classifying the indications for cesarean section and choosing three subgroups of infants for closer examination. The three groups were:

1. *Elective sections.* This group included the infants of mothers who had neither complicating medical conditions (such as heart disease or diabetes) nor pregnancy-related problems (such as antepartum hemorrhage). In this group of women, the decision for a cesarean section was made before the onset of labor, and the choice of anesthetic was based on the preference of the anesthesiologist and the parturient.
2. *Emergency sections.* This group included sections that had to be performed as quickly as possible and in which the anesthetic technique may have been dictated by the urgency of the situation, including fetal distress. Regional anesthesia would be limited to those cases in whom it was already established.
3. *Urgent sections.* These procedures were those that need to be performed quickly but for which a slight delay for establishment of regional anesthesia was acceptable. Included in this group are sections for dystocia or failure of labor to progress satisfactorily.

The remaining cases consisted of elective sections performed because of antepartum disease, emergency sections for indications such as cord prolapse or abruptio, and breech deliveries. These were excluded from the first analysis. The proportion of poor neonatal outcomes was compared (by χ^2 test) for each of the three groups by type of anesthesia, namely general versus regional. This allowed us to determine if the relationship between poor neonatal outcomes

Table 1. Number and Percentage of Infants by 1- and 5-Minute Apgar Scores after Cesarean Section (n = 3940)

Score	1-Minute Apgar *n*	1-Minute Apgar %	5-Minute Apgar *n*	5-Minute Apgar %
0–4	493	12.5	55	1.4
5–7	1065	27.0	250	6.3
8+	2382	60.5	3633	92.3
Missing	—		2	

and choice of anesthesia remained after considering specific indications for cesarean section.

For the second analysis, we used the entire group of 3940 infants (i.e., all indications) and examined the proportion of infants with low 1-minute Apgar score (4 or less) among the parturients with different characteristics to determine which of these were (significantly) associated with poor outcome using a χ^2 test.

To confirm the findings of the bivariate analysis, controlling for other risk factors for low Apgar score as determined in Table 2, we used a multiple logistic regression model (11). This enabled us to determine the relative risk of a poor neonatal outcome after delivery by cesarean section with general anesthesia as compared to regional anesthesia, all other factors being considered. More details on the statistical methods are found in the appendix.

Results

Among the 3940 infants delivered by cesarean section, 12.5% had 1-minute Apgar scores of 4 or less, and 1.4% had 5-minute Apgar scores of 4 or less (Table 1). Significantly associated with low 1-minute Apgar score (Table 2) were primiparity, grand multiparity, antepartum disease (including preeclampsia, diabetes mellitus, maternal heart disease, Rh isoimmunization, or early antepartum hemorrhage), a complicated labor, the presence of fetal distress, low birth weight, low gestational age, use of narcotics during labor, breech presentation, nonelective section, and general anesthesia. Not significant were maternal age over 40, multiple birth, use of oxytocin to induce or augment uterine contractions, failure to progress, gestational age 42 weeks or over, use of sedatives during labor, and year of birth.

There were 902 infants in the elective cesarean section group, 319 in the fetal distress group, and 1353 in the failure to progress group. The proportion of infants with poor neonatal outcomes in each of the three groups according to anesthetic technique is shown in Table 3. For all three groups, the proportion of infants with worse neonatal variables in all outcome comparisons was greater among those whose mothers received general anesthesia. The differences were statistically significant for the 1-minute Apgar scores for all three groups, for the 5-minute Apgar scores for the fetal distress and failure to progress groups, for need for oxygen by face mask for the elective and failure to progress groups, and for the percentage intubated for the fetal distress and failure to progress groups. The differences between neonatal death rates in the three groups were not statistically significant.

In the analysis shown in Table 3, the only factor controlled for in the comparison of anesthetic techniques was the indication for cesarean section. It is possible that other factors may have accounted for the poor outcomes in the general anesthesia group. Therefore, we used a multivariate technique (logistic regression) to determine the risk of having a poor neonatal outcome after general anesthesia as compared to regional anesthesia using a model that controlled for maternal age, parity, presence of antepartum disease, presence of labor complications, presence of fetal distress, gestational age, multiple birth, use of narcotics or sedatives during labor, elective versus nonelective section, and year of birth. We found that general anesthesia remained a significant risk for low 1-minute Apgar scores, and the risk was over three times that for regional anesthesia (relative odds = 3.13, 95% confidence interval 2.50–3.88). General anesthesia was still associated with a low 5-minute Apgar score (relative odds = 3.60, 95% confidence interval 1.81–7.00) and with the need for resuscitation (relative odds = 2.02, 95% confidence interval 1.39–2.90).

Discussion

The rate of low Apgar score at 1-minute in this study (Table 1) may appear much higher than in some other studies comparing regional and general anesthesia (1,4,8). The difference is probably due to selection of cases in previous studies. Our study included all cases having cesarean sections whereas other studies selected healthy parturients with no other risk factors. Our results, however, are comparable to other series of unselected cesarean section cases. Murphy et al. (12), for example, found that in the Cardiff Births Survey the rate of low Apgar score (score of 1–3) was 8.1–10.1% after elective section and 17.9–19.4% after emergency sections for the 1970–1974 and 1975–1979 periods.

In some of the previous studies of infants delivered by elective cesarean section, no significant dif-

Table 2. Factors Associated with 1-Minute Apgar Scores 0–4 after Cesarean Section (n = 3940)

Factor/reference	Low Apgar in cases with factor (%)	Low Apgar in reference cases (%)
Primiparity multiparity	13.9	10.5*
Grand multip/multip	23.5	10.5†
Antepartum disease yes/no	18.2	9.7†
Labor complications yes/no	14.4	11.7*
Fetal distress, yes/no	21.5	8.2†
Birth weight <2500 g/>2500 g	32.8	9.7†
Gestational age 34–37 weeks/38–42 weeks	19.2	9.1†
Gestational age <34 weeks/38–42 weeks	49.7	9.1†
Narcotics/no sedatives or narcotics	19.7	11.2*
Breech yes/no	20.1	11.9†
Nonelective section/elective	15.0	7.1†
General anesthesia/regional	22.4	8.9†
Maternal age >40/<40 years	11.1	12.3
Multiple birth/singleton	13.3	12.3
Oxytocin induction yes/no	12.4	12.2
Failure to progress yes/no	11.3	12.9
Gestational age 42+ weeks/38–42 weeks	11.8	9.1
Sedatives/no sedatives or narcotics	13.6	11.2
Year of birth 1978–80/1975–77	12.0	13.9
Year of birth 1981–83/1975–77	11.5	13.9

*P = ≤0.05;
†P = ≤0.0001.

Table 3. Neonatal Outcomes after Cesarean Sections by Anesthetic Technique

Indication for cesarean section	Anesthetic technique	Infants with 1-minute Apgar scores 0–4 (%)	Infants with minute Apgar scores 0–4 (%)	Neonates requiring oxygen by mask (%)	Neonates requiring tracheal intubation and ventilation (%)	Neonatal deaths (%)
Elective	Regional	2.0	0.2	10.1	1.7	0.5
	General	6.5*	0.4	16.3†	0.8	1.2
Fetal distress	Regional	18.5	2.8	19.7	19.0	3.3
	General	43.5†	8.3†	18.0	42.5‡	6.5
Failure to progress	Regional	9.1	0.5	14.5	10.4	0.7
	General	23.0‡	3.4†	24.0‡	19.6‡	1.4

*$P \le 0.05$;
†$P \le 0.01$;
‡$P \le 0.001$.

ferences in Apgar scores between infants of mothers who received general or epidural anesthesia were observed (1–4). These results have been interpreted by some to mean that anesthetic technique does not affect the condition of infants delivered by cesarean section. However, these studies were performed in a small number of selected elective cesarean section cases, and the results may not be applicable to the general obstetric population. In the study by Zagorzycki and Brinkman (4), 8.6% and 15.6% of the infants delivered under epidural and general anesthesia, respectively, had a 1-minute Apgar score less than 7. While the difference between the findings with general and epidural anesthesia was not statistically significant, a greater number of subjects and hence greater statistical power might have changed the interpretation of the data. James et al. (1) showed that 3 of the 20 infants from mothers who had general anesthesia had 1-minute Apgar minus color scores of 6 or less compared to none of 15 infants whose mothers had epidural anesthesia. The sample size (only 35 mothers undergoing elective cesarean section) was too small to detect a statistically significant difference.

Other investigators have reported better neonatal conditions among infants whose mothers received regional anesthesia. Apgar et al. (13) found that general anesthesia significantly increased the percentage of infants with scores of 0–4 among those delivered by elective cesarean section. Crawford and

Davies (7) studied 105 women undergoing elective cesarean section and found that Apgar minus color scores were better for infants (whether breech or vertex presentation) delivered with regional rather than general anesthesia. Abboud et al. (8) observed no difference in Apgar scores at 1 and 5 minutes among neonates delivered by cesarean section using general or regional anesthesia. They noted, however, that infants delivered after general anesthesia performed worse on some neurologic and adaptive capacity tests at 15 minutes and at 2 hours of age. Marx et al. (9), comparing the outcomes of infants whose mothers had undergone emergency cesarean section for fetal distress, found that 1-minute Apgar scores were significantly better following regional anesthesia.

In our study, which had a large sample size (n = 3940), we found that general anesthesia, whether for elective or emergency cesarean section, was an independent risk factor for low Apgar score after controlling for numerous other variables. Furthermore, our analysis of the elective cesarean group also found significantly better Apgar scores after regional anesthesia.

Although the infants born of mothers given general anesthesia had lower 1-minute Apgar scores and required more active respiratory resuscitation after birth, these infants were not necessarily asphyxiated. There was marked improvement in the 5-minute Apgar scores, and there was no significant difference in the neonatal death rates between the infants delivered by cesarean section under regional anesthesia and those under general anesthesia. Gregory et al. (14) and Bachman et al. (15) found MAC to be significantly lower in fetal lambs than in lambs more than 24 hours of age. These findings suggest that neonates immediately after birth may be quite sensitive to inhalation anesthetics so that those exposed to general anesthetic agents may be less vigorous at birth. After assisted respirations and expiration of the anesthetic agents, these infants appear to resemble other infants.

In summary, infants delivered by cesarean section under general anesthesia were more likely to be depressed and more likely to require active resuscitation than those delivered by cesarean section under regional anesthesia. However, with appropriate neonatal care, the choice of anesthetic technique did not appear to affect neonatal survival in the short term.

We thank Dr. Jane Evans for supplying the data on neonatal deaths.

Appendix

Definition and Categories of Variables Used in the Statistical Analyses

Low Apgar: one-minute or 5-minute Apgar score of 4 or less.

Gestational age: less than 34 weeks, 34–37 weeks, 38–42 weeks, 42 weeks or more.

Birth weight: less than 2500 g, more than 2500 g.

Maternal age: less than 40 years, more than 40 years.

Parity: nulliparous, multiparous (1–5 births), grand multiparous (6 or more births).

Antepartum factors: presence of at least one of preeclampsia, RH immunization, intrauterine growth retardation, heart disease, anemia, antepartum hemorrhage before 20 weeks, diabetes mellitus.

Oxytocin induction: use of oxytocin to initiate or augment uterine contractions (Yes or No).

Complications during labor: presence of at least one of cord around the neck, cord prolapse, high blood pressure during labor only, prolonged ruptured membranes.

Multiple birth: twins or triplets.

Sedatives: use of promethazine with or without narcotics.

Narcotics: use of narcotics alone or in combination with sedatives.

Anesthesia: epidural, general anesthesia (where general anesthesia includes that given after failed epidural).

Elective cesarean section: the decision for section was made before the onset of labor for whatever reason.

Fetal distress: presence of meconium staining and/or fetal heart decelerations or accelerations.

Failure to progress: No standardized definition was used. The variable was recorded if this diagnosis was given by attending obstetrician.

Statistical Methods

The multiple logistic model is a commonly used statistical tool that allows the researcher to examine a risk factor for a disease independently of other covariates that may also be associated with the disease or with the risk factor itself. In this study, the "disease" outcomes are low Apgar scores or the need for resuscitation. The logistic regression model seeks to answer the research question: What is the risk of having an adverse neonatal outcome after general anesthesia *as compared* to after delivery with regional anesthesia given the same antepartum medical conditions, the same parity, maternal age, labor complications, and so forth?

For the risk factor "low birth weight," the role of this variable in predicting a low Apgar score or need for resuscitation is complicated by the fact that many low-birth-weight infants are also of low gestational age. The two variables "low birth weight" and "low gestational age" are highly correlated with one another (r = 0.60 in this study). If two covariates are highly correlated with one another, then the variance of the estimated β coefficients from the logistic regression will be markedly altered by including "redundant" variables in the model (16). This problem, known as multicollinearity, can be avoided by choosing one variable from a cluster of "similar" variables. We chose a variable if it had good explanatory power relative to the alternatives or was of clinical importance. For example, "gestational age" was chosen over "low birth weight" because gestational age is known in advance of the birth whereas birth weight often is not known. (Birth weight is actually more of an outcome variable than a "predictor.")

Thus for the multiple logistic regression modeling, we used a two-step process. First each potential risk factor was tested for an association with the dependent variable by a χ^2 test. We examined each variable in a variety of ways and found that as various categorizations of the variables (continuous, categorical, or dichotomous) did not affect the final results, dummy variables were used to simplify interpretation. Then the correlation coefficients between risk factors were determined and variables excluded to avoid a collinearity problem. Finally all variables were entered (whether significant or not in the univariate analysis) into the final model. Separate models were fit for low 1-minute Apgar score, low 5-minute Apgar score, and need for resuscitation.

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Surgical Repair of Hip Fractures Using Continuous Spinal Anesthesia:

Comparison of Hypobaric Solutions of Tetracaine and Bupivacaine

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VAN GESSEL EF, FORSTER A, GAMULIN Z. Surgical repair of hip fractures using continuous spinal anesthesia: comparison of hypobaric solutions of tetracaine and bupivacaine. Anesth Analg 1989;68:276–81.

The aim of this study was to compare hypobaric solutions of tetracaine and bupivacaine in 30 geriatric patients undergoing surgical repair of hip fractures while under continuous spinal anesthesia. Tetracaine 1% and bupivacaine 0.5% were mixed with distilled water to prepare hypobaric 0.25% solutions. In a double-blind fashion, all patients received 3 ml (7.5 mg) of either solution in the lateral decubitus position with the operated side up, the table being kept horizontal for 30 minutes after injection. The mean highest sensory levels in both groups, and in both operated and non-operated sides in the same group, were comparable, ranging between T7 and T8.5. Duration of analgesia was 134 minutes with tetracaine and 130 minutes with bupivacaine (NS). In both groups, motor blockade was satisfactory in 29/30 patients on the operated side. The frequency of a decrease in systolic blood pressure of more than 30% was similar in the two groups. The authors conclude that hypopobaric solutions of both tetracaine and bupivacaine are suitable for surgical repair of hip fractures in geriatric patients and produce comparable anesthetic and hemodynamic effects.

Key Words: ANESTHETIC TECHNIQUES: spinal, continuous hypobaric. ANESTHESIA, LOCAL: tetracaine, bupivacaine. ANESTHESIA, orthopedic.

Continuous spinal anesthesia (CSA), a technique in use since the 1940s (1), has recently been updated in our institution and is now the main type of anesthesia for hip fracture surgery in elderly patients. This technique allows one to titrate and thus to reduce the dosage of local anesthetics, and provides a more adequate analgesia with a lower level of sympathetic blockade, minimizing arterial hypotension and bradycardia.

Since in our institution surgical repair of fractured hips is performed with the patient in the lateral or the semi-lateral decubitus position, the use of hypobaric solutions of local anesthetics should theoretically allow a more selective sensory and sympathetic blockade of the operated limb. In addition, with this technique, anesthesia and surgery can be performed in the same position, thus avoiding unnecessary and painful postural changes.

Tetracaine is the drug generally advocated today for hypobaric single and continuous spinal anesthesia (2,3). Hyper- and isobaric bupivacaine have been recently introduced for single injection spinal anesthesia (4–6). However, to our knowledge, the administration of hypobaric bupivacaine has not yet been reported. This study was designed to determine the anesthetic properties of hypobaric bupivacaine in CSA and to compare it with hypobaric tetracaine.

Methods

After institutional approval, informed consent was obtained from 30 patients, more than 70 years of age, scheduled for surgical repair of femoral neck or trochanteric fractures under CSA. These patients were randomly allocated into two groups: tetracaine and bupivacaine.

During the pre-anesthetic visit, a central venous pressure line and an indwelling urinary catheter were inserted to assess, and, when necessary, to correct hypovolemia with a crystalloid solution or, when the hematocrit was less than 35%, with blood. Blood volume was considered optimal when urinary output

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was at least 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ during the 2 hours preceeding anesthesia.

Preoperative medication consisted of i.m. meperidine 0.5 mg/kg and promethazine 0.25 mg/kg, one hour before the arrival in the operating room; heart rate and arterial pressure were then measured with a non-invasive automatic blood pressure device (Minimap) and the electrocardiogram (ECG) was continuously monitored. Preanesthetic hydration consisted of 10 ml/kg of a crystalloid solution; immediately after the injection of the local anesthetic, another 5 ml/kg were given over 30 minutes. Thereafter fluids were administered on the basis of changes in arterial pressure, central venous pressure and urinary output. Blood loss was replaced with a crystalloid solution on a 3 per 1 cc basis until estimated or measured hematocrit reached 35%. Further losses were replaced by blood.

CSA was performed in the lateral decubitus position with the operated side up. An 18 gauge Tuohy needle was inserted at the L2-L3 or L3-L4 interspace using the midline approach. After entering the subarachnoid space, a 20 gauge catheter was introduced cephalad for approximately 3 to 4 cm. Patients then received in a double blind fashion 3 ml of one of the two anesthetic solutions injected over a three minute period through the catheter. The rate of injection was 1 ml over 15 seconds followed by a pause of 45 seconds. The two hypobaric anesthetic solutions were prepared as follows: -Solution 1—2 ml (20 mg) of tetracaine 1% diluted with distilled water up to 8 ml, i.e., 2.5 mg/ml with a measured density of 0.991 at 37°C and a calculated baricity of 0.9907; -solution 2—4 ml (20 mg) of bupivacaine 0.5% diluted with distilled water up to 8 ml, i.e., 2.5 mg/ml with a measured density of 0.992 at 37°C and a calculated baricity of 0.9917. To calculate the baricities the mean value of density of cerebrospinal fluid used was 1.0003 at 37°C as previously reported (7).

The operating table was kept in a horizontal position and the patients in lateral decubitus position during the first 30 minutes before surgery to assess sensory and motor blockades in all patients under similar conditions. Thereafter, surgery was performed with the patients in lateral or semi-lateral decubitus position as required.

The following were measured every three minutes during the first 30 minutes after the injection: 1) upper level of sensory blockade, evaluated by the pin-prick test, on both sides on the anterior axillary line; a level lower than T10 on the operated side was considered insufficient; 2) quality of motor blockade on both sides according to a modified Bromage scale (ranging from 0, indicating no motor blockade, to III, indicating complete motor blockade) (8); a motor blockade of grade II to III on the operated side was considered adequate for surgical conditions; and 3) elapsed time from injection to disappearance of pain at the fracture site (subjective analgesia), upon slight passive hip movement.

The following were measured throughout the operation: duration of sensory blockade, i.e., when pain reappeared at the operative site, requiring the reinjection of 1 ml of the anesthetic solution; incidence and amount of vasopressors and/or anticholinergics used; total amounts of crystalloids and blood transfused; quality of muscle relaxation evaluated subjectively by the surgeons; arterial pressure and heart rate measured before the injection, every minute thereafter for 15 minutes and subsequently every 2.5 minutes until the end of the surgery; and central venous pressure measured every 15 minutes and urinary output every 30 minutes.

The frequency of clinically important hypotension, defined as a decrease in systolic arterial pressure of 30% of more below preoperative baseline levels, as well as frequency of decreases in heart rate of more than 20% were recorded. These hemodynamic changes were treated with intravenous mephentermine sulfate 7.5 mg and intravenous atropine sulfate 0.5 mg, respectively. Discomfort related to lateral decubitus position was treated with fentanyl 0.05 mg and/or etomidate 2 mg or midazolam 1.5 mg i.v. as clinically required.

In the recovery room, the position of the intrathecal catheter was determined radiologically after its opacification with 1 ml of Iopamiro 370(R). All patients were clinically assessed daily during their stay in the hospital until discharge. Mean duration of hospitalization was recorded, as was mortality.

Unpaired *t*-tests and chi square tests were used as required to compare the two groups. Paired *t*-test was used to compare variables in the same group. Data with *P* values equal or smaller than 0.05 were considered statistically significant. All results are expressed as mean ± SEM.

Results

Fifteen patients were allocated to each group. As summarized in Table 1, age, ASA physical status, male/female ratio and surgical procedure were comparable in both groups. Pre-anesthesic mean arterial pressure (MAP), heart rate (HR), central venous pressure, urinary output and hematocrit were also comparable (Table 2). Postoperative radiologic controls indicated that all catheters were directed cranially and placed at a mean level of L2 (range L1 to L3 for tetracaine and T12 to L3 for bupivacaine).

Table 1. Patients Characteristics and Surgical Procedures

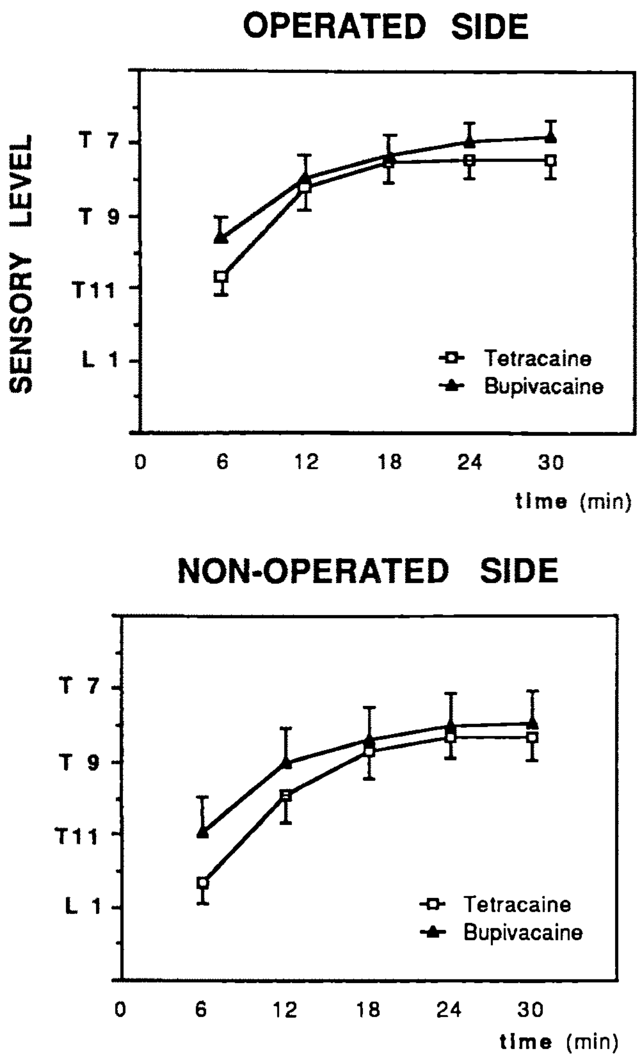
	Tetracaine	Bupivacaine
Age (years) (x̄ ± SEM)	86 ± 2	84 ± 1
Asa status	II 5 III 9 IV 1	II 7 III 7 IV 1
Male/female ratio	2/13	2/13
Surgical procedure	DHS 9 PHP 6	DHS 8 PHP 7

DHS = Dynamic Hip Screw/PHP = Partial Hip Prosthesis.

Table 2. Hemodynamic Variables Measured Before Anesthesia (x̄ ± SEM)

	Tetracaine	Bupivacaine
Mean arterial pressure (mmHg)	106 ± 5	107 ± 5
Heart rate (beats/min)	93 ± 3	89 ± 4
Central venous pressure (cmH_2O)	6 ± 1	6 ± 1
Urinary output (ml/H)	92 ± 18	91 ± 19
Hematocrit (%)	37 ± 1	39.0 ± 1.5

Sensory blockade: The mean onset of "subjective analgesia" as defined was significantly shorter ($P = 0.001$) with tetracaine (3.6 ± 0.3 minutes) than with bupivacaine (4.4 ± 0.6 minutes). Cephalad spread of sensory blockade, assessed by pin-prick, on both sides is illustrated in Figure 1; as seen, the sensory levels on the operative side as well as the non-operative side were comparable in the two groups at all times. Also, no difference was found between the mean highest sensory levels which on the operated side were T7.5 ± 0.6 for tetracaine and T7.0 ± 0.5 for bupivacaine, and on the non-operated side T8.5 ± 0.7 and T8.0 ± 0.8, respectively. The mean time to reach these levels was also comparable: on the operated side 13.0 ± 1.1 minutes for tetracaine and 16.0 ± 1.3 minutes for bupivacaine; on the non-operated side 16.0 ± 1.3 minutes and 18.0 ± 1.2 minutes respectively. No difference was found between highest sensory levels on the operated and non-operated sides of the patients receiving the same drug.


OPERATED SIDE

NON-OPERATED SIDE

Figure 1. Spread of sensory level in the first 30 minutes after administration of tetracaine and bupivacaine, on operated and non-operated sides (x̄ ± SEM).

Table 3. Maximal Degree of Motor Blockade

	Operated limb		Non-operated limb	
	Tetracaine	Bupivacaine	Tetracaine	Bupivacaine
Grade 0 and I (No. of patients)	1	0	6	6
Grade II and III (No. of patients)	14	15	9	9

NS between groups.
$P < 0.05$ between operated and non-operated side within the same group. Grade 0 = no motor blockade; Grade I = inability to raise extended leg (able to move feet and knees); Grade II = inability to flex knees (able to move feet only); Grade III = inability to move feet and knees.

Motor blockade: The number of patients with grade II to III motor blockade in both limbs is shown in Table 3. On the operated side, a similar number of patients in both groups had grade II or III, and the mean time to induce such blockade was 16.0 ± 1.4 minutes with tetracaine and 15.0 ± 1.9 minutes with bupivacaine (NS). However, unlike sensory blockade, in both groups a difference in level of maximal motor blockade existed between the operated and non-operated sides ($P = 0.04$). Maximal motor blockade on the non-operated side was achieved in 14.0 ± 1.7 minutes with tetracaine and 15.0 ± 2.6 minutes with bupivacaine (NS).

Table 4. Hemodynamic Changes in the First 30 Minutes After Injection of Anesthetic Solutions ($\bar{x}$ ± SEM)

	Tetracaine	Bupivacaine
Maximal changes from pre-anesthetic baseline values in:		
MAP (%)	−29 ± 3	−32 ± 4
HR (%)	−6.5 ± 2.0	−6.8 ± 2.0
Time to reach maximal changes in:		
MAP (min)	17 ± 2	16 ± 2
HR (min)	15 ± 2	18 ± 3
No. patients given mephentermine sulfate	10	7
Mean dosage (mg) mephentermine	10.5 ± 3.0	8.0 ± 3.0

MAP = Mean Arterial Pressure/HR = Heart Rate.

Hemodynamic changes: The mean changes in MAP and heart rate during the first 30 minutes after injection of the anesthetic solution, as well as number of patients given mephentermine sulfate and its mean total dosage are reported in Table 4. There were no significant differences between the two groups.

Thirty minutes after spinal injection, five patients in the tetracaine group (4 because of a sensory level lower than T10 and one because of insufficient motor blockade) and one patient in the bupivacaine group (sensory level lower than T10) required one additional ml of drug injected through the catheter (P = 0.084), to provide satisfactory operating conditions. These patients were not considered in determination of the duration of sensory blockade.

The duration of sensory blockade as defined averaged 134 ± 8 minutes with tetracaine (n = 10) and 130 ± 10 minutes with bupivacaine (n = 14) (NS). After the thirty minutes study period, during surgical preparation and surgery itself, mean values of central venous pressure and urinary output were comparable in the two groups at all times. Throughout the study, the estimated blood losses for all patients were 403 ± 244 ml in the tetracaine group and 356 ± 180 ml in the bupivacaine group (NS); 10 patients in each group received blood transfusions, at a mean volume of 535 ± 227 ml and 425 ± 210 ml, respectively (NS). The amount of crystalloids administered during the study was 2400 ± 280 ml in the tetracaine group and 2350 ± 233 ml in the bupivacaine group (NS). The number of patients receiving mephentermine sulfate was 13 of 15 in the tetracaine group and 8 of 15 in the bupivacaine group (P = 0.054). Six patients receiving tetracaine and eight receiving bupivacaine required either etomidate (dose ranging from 4 to 7 mg) or midazolam (dose ranging from 3 to 4 mg) for sedation. Fentanyl 0.05 mg was given to one patient in the tetracaine group and to two in the bupivacaine group. Finally, in all patients, one or two re-injections of local anesthetics through the catheter were required during surgery, which lasted 91.5 ± 26 min in the tetracaine group and 92 ± 23 min in the bupivacaine group.

The quality of surgical anesthesia was judged satisfactory by the surgeons in all patients. One patient receiving tetracaine developed a post-spinal headache, which lasted 7 days and resolved with conservative treatment. Overall mortality was 23% (3/15 with tetracaine; 4/15 with bupivacaine, NS); all deaths occurred between 48 hours and 23 days after the operation, and were due to co-existing diseases. Mean duration of hospital stay was 24 ± 3 days for patients in the tetracaine group and 21 ± 2 days for patients in the bupivacaine group (NS).

Discussion

This study demonstrates that hypobaric bupivacaine is as reliable and effective as hypobaric tetracaine when CSA is used for surgery of hip fractures in geriatric patients. In this study, all anesthetic and hemodynamic data were comparable except for the onset of subjective analgesia, which was statistically shorter for tetracaine, but clinically irrelevant.

Comparison of our data with data from the literature is difficult because among the publications having compared these two drugs (4,5,8–14), only few (4,5,12,14) were conducted using identical dosage, volume and concentration of tetracaine and bupivacaine; Pflug et al. and Moore studied these two drugs (4,5) at a dosage similar to that used in our study (7.5 mg), but in their studies both solutions were hyperbaric and the volume injected was 1 ml at a concentration of 0.75%. Furthermore, it has been reported (15) that, for a same dosage and volume, the spread and duration of analgesia as well as quality of motor blockade are different when hyper- and hypobaric solutions of tetracaine are administered. We will nevertheless discuss and compare our data with the studies by Pflug et al. and by Moore (4,5), since studies comparing hypobaric solutions of these two drugs have not yet been published.

In our study, the spread and upper level of sensory blockade were similar with tetracaine and bupivacaine on both sides; similarly, Pflug et al. and Moore (4,5) found no difference in the levels obtained with the same dosage of hyperbaric solutions of these anesthetics. Despite the fact that these two studies used different and indirect criteria to determine the duration of analgesia, neither found a difference in duration between 7.5 mg of hyperbaric tetracaine or bupivacaine. In our study, the duration of sensory blockade, assessed by the appearance of intraoperative pain, was comparable with both hypobaric drugs. We consider this assessment, which can be used only during CSA, as the most accurate and reliable since all patients had similar incisions.

Motor blockade was satisfactory on the operative side in both groups; 29 of 30 patients had either grade II or III motor blockade on Bromage scale. This is in agreement with Pflug et al. (4) but not with Moore (5) who found that 7.5 mg of hyperbaric tetracaine provided a more profound and longer lasting motor blockade. The duration of motor blockade was not assessed in our study in order not to interfere with surgery. However re-injection of drug was never required because of either inadequate motor blockade or patient movement.

No anesthetic failure was observed in our study. However, after the initial injection of 3 ml of hypobaric drug, unsatisfactory anesthesia, i.e., a sensory level lower than T10 and a motor blockade less than grade II on the Bromage scale, was observed in five patients given tetracaine and one patient given bupivacaine ($P = 0.084$). We think that this trend cannot be attributed to differences in site of injection since the mean level of catheter placement was similar for both groups. It may nevertheless indicate that 3 ml (7.5 mg) of hypobaric bupivacaine is more predictable and reliable than the same amount of tetracaine, especially when a single injection spinal anesthesia is planned. Moore's results (5) are in agreement with this finding since he encountered a significantly higher percentage of unsatisfactory analgesia with 7.5 mg of tetracaine than with the same dosage of bupivacaine. We feel, however, that further investigations with a larger number of patients are necessary to confirm or negate the greater predictability of hypobaric bupivacaine observed in our study.

Our data for the first 30 minutes after the initial injection of anesthetics show that the decrease in MAP, and consequently the number of patients requiring mephentermine sulfate, were comparable in the two groups. However, during the entire study, which lasted approximately 150 to 200 minutes, 13 of 15 patients receiving tetracaine and eight of 15 patients receiving bupivacaine required mephentermine sulfate ($P = 0.054$). This difference may be misleading and does not allow one to conclude that the hemodynamic effects of the drugs are different since numerous other factors, i.e. frequency of anesthetic re-injections, blood volume status at time of drug re-injection, etc., probably played important roles. The lack of difference in hemodynamic effects between the two drugs is confirmed by Pflug et al. and Moore (4,5) but is not in agreement with a recent study (14) in which hypotension was more profound with 3 ml of a 0.5% solution of hyperbaric tetracaine than with an identical dosage of bupivacaine.

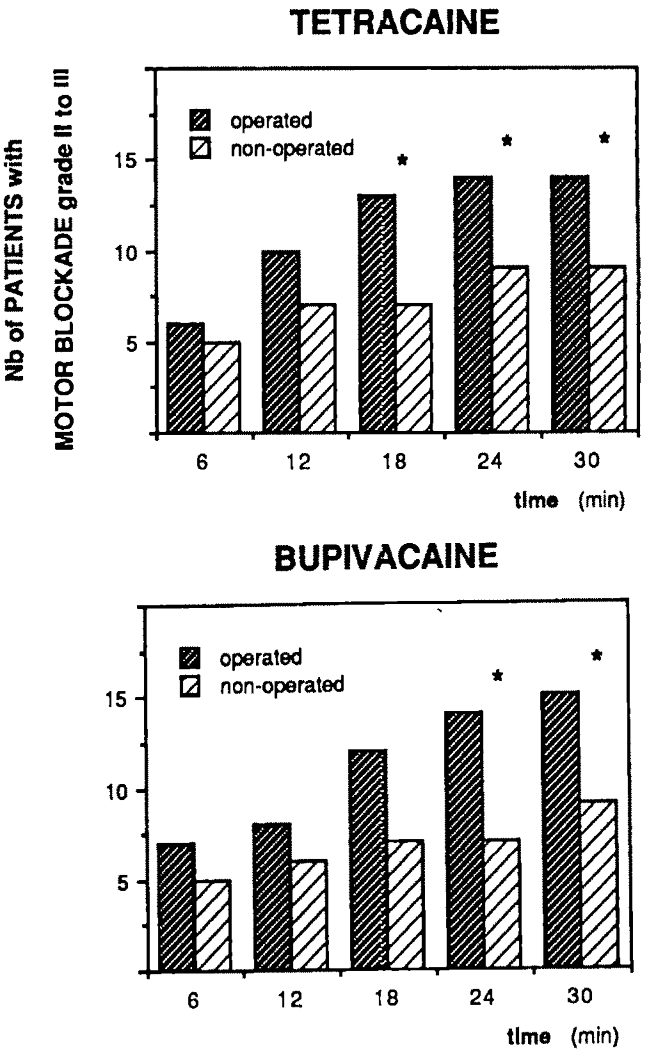


Figure 2. Number of patients with grade II to III motor blockade on operated and nonoperated sides during the first 30 minutes after administration of tetracaine and bupivacaine (* = $P < 0.05$, comparison between operated and non-operated sides).

Hypobaric spinal anesthesia is rarely reported in the literature (3) and, though always mentioned as a possible indication for lower limb surgery (16), is infrequently administered. Our data suggest that the administration of either hypobaric tetracaine or bupivacaine in CSA is suitable and reliable for surgical treatment of fractured hips in elderly patients. One of the theoretical advantages of this technique should be the ability to produce a unilateral analgesia with a more selective sympathetic blockade and less hemodynamic consequences. Unfortunately, after the initial injection of 3 ml, only the motor blockade was unilateral (Fig. 2) and, although a significant difference was noted during the first minutes of segmental spread, the final sensory level (Fig. 3) was similar on both sides. Since, according to Greene (7) all anes-

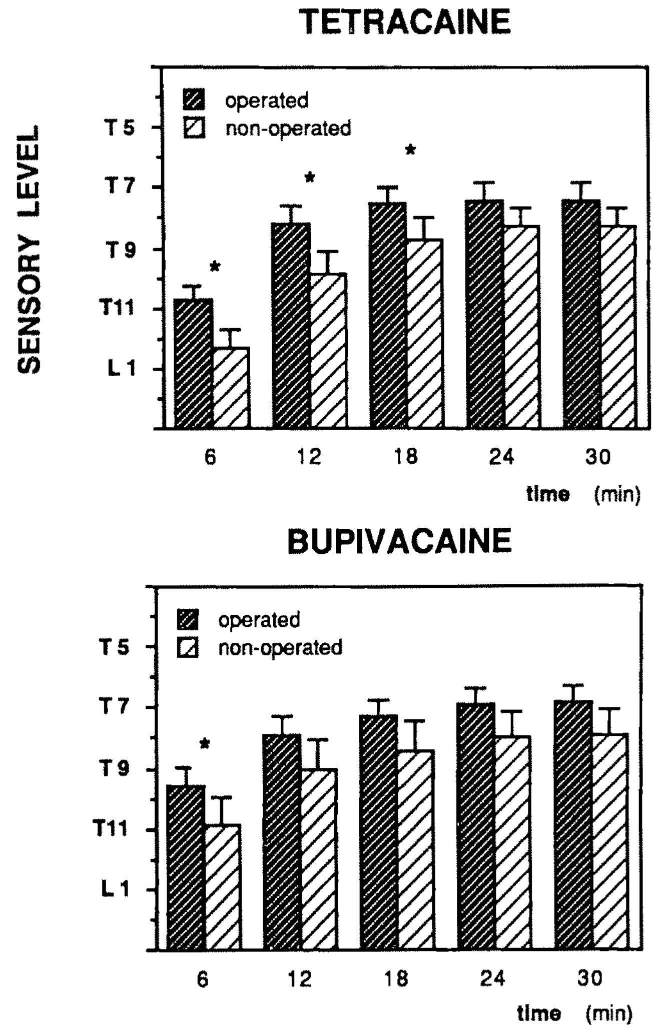


Figure 3. Comparison of spread of sensory level between operated and non-operated sides during the first 30 minutes after administration of tetracaine and bupivacaine ($\bar{x} \pm$ SEM) (* = $P < 0.05$, comparison between operated and non-operated sides).

thetic solutions with baricities of less than 0.999 are considered predictably hypobaric in all patients, this finding could be due to the mode of injection; in our study, the administration rate was as described previously 1 ml in 15 seconds (0.06 ml/sec) followed by a 45-second pause, but it has been recently suggested that a unilateral analgesia can be obtained with hypobaric tetracaine if the drug is continuously administered at a rate of 0.02 ml/sec (1 ml in 50 seconds) (17). The injection of a more hypobaric solution or the use of a smaller volume could possibly also lead to a better differential spread. We feel that the technique of hypobaric CSA should be further investigated.

Within 48 hours, all patients were mobilized and only one patient developed a postspinal headache. This low rate of complication was confirmed in a recent study (18), in which, in a much younger population, only one of 117 had postspinal headaches.

Both hypobaric tetracaine and bupivacaine, when used in CSA, produced suitable anesthesia for surgical treatment of fractured hips in geriatric patients and were associated with comparable hemodynamic effects.

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Midazolam-Morphine Sedative Interaction in Patients

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The sedative effects of midazolam, morphine, and their combination were studied in ASA physical status I and II patients. The visual analog method was used to determine sedative effect. A self-rated score of 50 mm or more on a 100-mm line was regarded as a positive response to the treatment. The dose-response curves for midazolam, morphine, and their combination (each in a group of 30 patients) were determined by probit procedure and compared with isobolographic and algebraic (fractional) analyses. Interactions between midazolam and morphine when used to produce sedation represent summation, not synergism.

Key Words: ANESTHETICS, intravenous—midazolam. ANALGESICS—morphine. INTERACTIONS, drugs—opioids, benzodiazepines.

Combinations of benzodiazepines and opioid drugs are used commonly for intravenous sedation (1–4). Life-threatening complications during midazolam-induced conscious sedation in patients receiving opioid drugs have been reported (5), which indicates the importance of the problem of midazolam-opioid sedative interaction. Several authors have demonstrated that opioid drugs strengthen the hypnotic effect of benzodiazepines (6–8), and benzodiazepines potentiate the anesthetic effect of opioids (9). These studies, however, did not indicate whether the observed results reflected synergism or simple summation of the effects. The aim of the present study was to define the type of interaction involved when a combination of midazolam and morphine is used to produce sedation.

Methods

Ninety unpremedicated ASA physical status I or II adult female patients schedule for diagnostic curettage or other minor surgeries participated in the study, which was approved by the Institutional Human Investigation Committee. Patients who had taken or received benzodiazepines, opioid drugs, or other sedative agents within one month of the investigation were excluded from the study. Subjects were lying on a bed in a quiet room where they remained for the duration of the study. An intravenous catheter for drug injections was inserted into the antecubital vein and kept patent with a slow infusion of normal saline solution. The sedative effect was determined with the use of visual analog self-rating method as described by Hommer et al. (10). The visual analog scale consisted of a 100-mm line without gradation with the word "alert" at the left end and at the right, the word "sleepy." The patients were told to indicate how they felt at the moment by placing a mark perpendicular to the line. The scales were scored by measuring the distance (in millimeters) of the perpendicular mark from the left end of the line.

Patients were randomly assigned to one of three groups to be given either midazolam, morphine, or midazolam-morphine. Each group consisted of 30 patients divided into six subgroups of five patients each with predetermined doses of drugs in each subgroup. Each patient received two intravenous injections with a 10-minute interval between them. The midazolam group was given normal saline first and then midazolam; the morphine group received morphine first, then saline; and the midazolam-morphine group received morphine first, then midazolam. Prior to the first injection and 5 minutes after the second, each patient was asked to mark the visual

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analog line. Times between injections of drugs and determination of the sedative effect were based on the times to peak effect for these agents (15 minutes for morphine and 5 minutes for midazolam). With combined drug administration, both drugs were injected so that synchronization of the peak effects would occur. These time intervals were selected on the basis of a preliminary study. The self-rated sedation was checked by an investigator unaware of what drug(s) or dose(s) was used (double-blind method). Midazolam hydrochloride and morphine hydrochloride were used. Doses of both drugs were expressed in terms of the salt.

The following predetermined doses of drugs each in a subgroup of five patients were administered: in the midazolam group (mg·kg^{-1}): 0.01, 0.02, 0.03, 0.04, 0.05, 0.07; in the morphine group (mg·kg^{-1}): 0.03, 0.04, 0.06, 0.08, 0.10, 0.12. In the midazolam-morphine group, doses of both agents were changed from one subgroup to another with the fixed dose ratio of 1:2 (2 mg of morphine per 1 mg of midazolam). This ratio was determined on the basis of the preliminary study and reflects relative sedative potencies of these agents. As a result, the following doses were administered in the midazolam-morphine group (mg·kg^{-1}): 0.003 and 0.006; 0.005 and 0.010; 0.008 and 0.016; 0.012 and 0.024; 0.02 and 0.04; 0.03 and 0.06.

As an endpoint for determining the dose-response curves, a sedation score of 50 mm or more was used, allowing us to obtain a quantal curve of a graded type of response to an agent (11). As a result, the construction of the dose-response curves and determination of the ED_{50} values were based on probit procedure (12). To define the type of interaction between midazolam and morphine, isobolographic (13) and algebraic (fractional) (14) analyses were used (ED_{50} level). With isobolographic analysis, ED_{50} values from all groups of patients were plotted in the form of an isobol. Single-drug ED_{50} points were placed on the dose coordinates of the isobologram and a combined ED_{50} point in the dose field. The deviation of a combined ED_{50} point from an additive line (a straight line joining single-drug ED_{50} points) was measured as the length along a line running from the point in question to the additive line perpendicular to it. The standard error of this distance was computed by the propagation of error method (15), and error estimates from a combined ED_{50} point, as well as single-drug ED_{50} points, were used. An approximate *t*-test used to test the assumption of additivity was then obtained as the ratio of the measured distance to its standard error (16). Algebraic (fractional) analysis was based on the expression of doses of the midazolam and morphine components of the combination (Ac and Bc) as fractions of the doses of these drugs that produce the same effect when given separately (Ac/As and Bc/Bs). The sum of fractional doses equals to 1.0 in addition, as expressed by the following equation:

$$\frac{Ac}{As} + \frac{Bc}{Bs} = 1.0$$

In synergism, the sum of fractional doses is less than 1.0, and, in antagonism, it is more than 1.0 (Table 2). Statistical validation for algebraic (fractional) analysis duplicated that for isobolographic analysis.

Table 1. Characteristics of Patients (Mean ± SD)

Variable	Midazolam	Morphine	Midazolam-Morphine
Age (years)	33 ± 10	34 ± 12	36 ± 9
Weight (kg)	66 ± 14	64 ± 10	66 ± 15
Number of patients (all female)	30	30	30

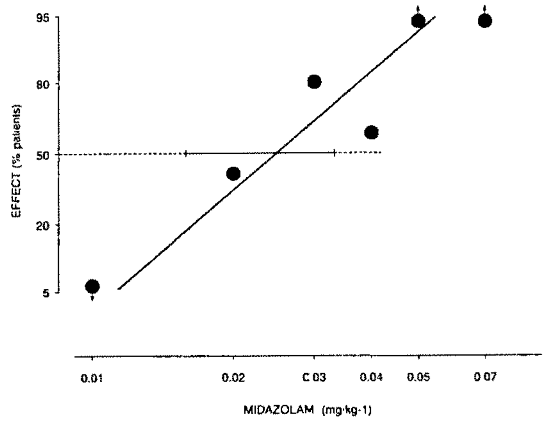

Figure 1. Midazolam quantal dose-response curve for sedation. Along the vertical axis, the percentage of patients (on a probit scale) with a self-rated score of 50 mm and more using a 100-mm visual analog line for sedation (alert-sleepy). Along the horizontal axis, the doses of midazolam (on a log scale). Each dot represents a subgroup of five patients at the indicated dosage. A horizontal line at the ED_{50} level indicates 95% confidence limits.

Results

The study groups were comparable with respect to age and weight (Table 1). The sedative dose-response curve for midazolam is presented in Figure 1. The midazolam ED_{50} value obtained from this curve was 0.025 mg·kg^{-1} (95% confidence limits, 0.014–0.033

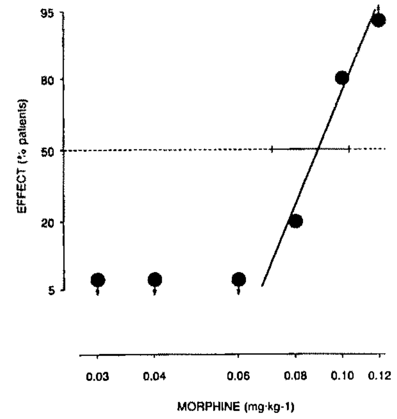

Figure 2. Morphine quantal dose-response curve for sedation. For details see Figure 1.

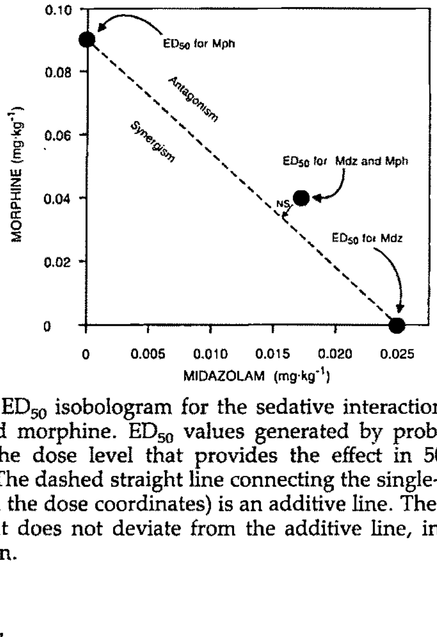

Figure 3. ED_{50} isobologram for the sedative interaction of midazolam and morphine. ED_{50} values generated by probit analysis indicate the dose level that provides the effect in 50% of the patients. The dashed straight line connecting the single-drug ED_{50} points (on the dose coordinates) is an additive line. The combined ED_{50} point does not deviate from the additive line, indicating a summation.

$mg{\cdot}kg^{-1}$). Figure 2 illustrates the sedative dose-response curve for morphine with an ED_{50} value of 0.089 $mg{\cdot}kg^{-1}$ (95% confidence limits, 0.072–0.105 $mg{\cdot}kg^{-1}$). Comparison of the midazolam and morphine dose-response curves shows that the slope of the midazolam curve is flatter than that for morphine. Probit:log dose ratio reflecting the degree of the slope was 4.9 for midazolam and 18.8 for morphine. The difference in the slopes was statistically significant ($P < 0.05$).

The midazolam-morphine isobologram is presented in Figure 3. The combined ED_{50} point for sedation did not deviate to any significant extent from the additive line (joining the single-drug ED_{50} points), indicating a summation of effects. Fractional analysis of the midazolam-morphine sedative interaction is presented in Table 2. In combination, the sum of the fractional doses was not different from a single-drug fractional dose.

Discussion

The midazolam ED_{50} value for sedation with the endpoint used in the present study was 0.025 $mg{\cdot}kg^{-1}$ which constitutes approximately 1/8 of the midazolam ED_{50} value for hypnotic effect (0.19 $mg{\cdot}kg^{-1}$ for abolition of the response to verbal command in the similar patient population) (17). If 1 $mg{\cdot}kg^{-1}$ is regarded as a minimal anesthetic dose of morphine (18), the ED_{50} value for sedation obtained in the present study (0.09 $mg{\cdot}kg^{-1}$) would constitute a fraction of the morphine anesthetic dose which is similar to that for midazolam. A marked difference in the slopes of the sedative dose-response curves was found for morphine and midazolam (18.8 vs 4.9, $P < 0.05$). The flatter dose-response curve for midazolam (Fig. 1) reflects a pronounced interindividual variability in response typical for various effects of this agent (19).

The isobolographic and algebraic analyses used in the present study demonstrated that the midazolam-morphine sedative interaction resulted in an additive effect (summation), not synergism. This means that the requirement for one agent to produce a certain degree of sedation is decreased by another agent, but only to a degree equivalent to the sedative dose of the latter.

Respiratory and cardiac arrests described in patients who received midazolam in combination with opioids for conscious sedation (5) might be due to the excessive CNS depression caused by a synergistic midazolam-opioid interaction. The results of the present study indicate that with sedative doses the interaction between midazolam and morphine does not go beyond simple summation of the effects. However, this does not exclude the possibility that the interaction between midazolam and morphine in relation to respiratory depression or other adverse effects results in a profound synergism. It is possible to suggest that midazolam-opioid interactions may be different even in relation to such similar effects as sedation and hypnosis. In the study by Gamble et al. (6), 10 out of 20 patients did not open their eyes on command 5 minutes after midazolam administration (0.3 $mg{\cdot}kg^{-1}$, i.v.) and 17 out of 20 patients reached the same endpoint when midazolam (also 0.3 $mg{\cdot}kg^{-1}$) was given with "light opiate" premedication (meperidine 50–75 mg per patient, i.m.). At the same time, the number of patients who were not at

Table 2. Midazolam-Morphine Sedative Interaction

	Equi-Effective I.V. Doses (ED$_{50}$) fraction mg/kg		
Group	Midazolam Component	Morphine Component	Sum of Fractions
Midazolam	1.00 0.025 (0.014, 0.033)*	0.00	1.00
Morphine	0.00	1.00 0.089 (0.072, 0.105)	1.00
Midazolam and Morphine	0.68 0.017 (0.011, 0.038)	0.39 0.035 (0.023, 0.077)	1.07**

* - Confidence limits in parentheses.
** - Deviation from additivity was statistically insignificant.

least very drowsy did not significantly change: three out of 20 without opiate premedication and two out of 20 with it. These results suggest that meperidine does not increase the incidence of transition from light to profound midazolam-induced sedation to such an extent as that from profound sedation to unconsciousness. For comparison, it should be mentioned that in a study of postoperative sedation, alfentanil was found to strengthen the sedative but not the amnesic effect of midazolam (20). In conclusion, the midazolam-morphine sedative interaction represents summation of effects, not synergism.

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Left Ventricular Oxygen Tensions in Dogs During Coronary Vasodilation by Enflurane, Isoflurane and Dipyridamole

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HABAZETTL H, CONZEN PF, HOBBHAHN J, GRANETZNY T, GOETZ AE, PETER K, BRENDEL W. Left ventricular oxygen tensions in dogs during coronary vasodilation by enflurane, isoflurane, and dipyridamole. Anesth Analg 1989;68:286–94.

The purpose of this study was to investigate the effects of the anesthetics enflurane and isoflurane and of the coronary vasodilator dipyridamole on myocardial oxygen balance and myocardial tissue oxygen tensions. The studies were performed in 24 open-chest dogs during basal anesthesia with a narcotic. Myocardial blood flow (MBF) was measured using radioactive microspheres, myocardial surface tissue PO_2 *by means of a platinum multiwire surface electrode. One control group and three experimental groups were studied: enflurane (1.1 vol%), isoflurane (0.7 vol%, both end-tidal concentrations), and dipyridamole (0.4 mg/kg). Mean arterial pressure significantly decreased to an average of 70 mm Hg in all three experimental groups. Although MBF was unchanged during enflurane (−18%) and isoflurane (+20%), it increased during dipyridamole (+304%* $p < 0.05$ *vs baseline and control, enflurane, and isoflurane groups). Myocardial oxygen consumption decreased significantly during enflurane and isoflurane but remained unchanged during dipyridamole. Thus, the ratio between myocardial oxygen delivery and consumption increased 6% with enflurane (*$p < 0.05$ *vs baseline), 47% with isoflurane (*$p < 0.05$ *vs baseline and control group) and 280% with dipyridamole (*$p < 0.05$ *vs baseline and control, enflurane, and isoflurane groups). Coronary venous* PO_2 *remained unchanged during enflurane but increased significantly during isoflurane and dipyridamole. Left ventricular surface tissue* PO_2 *was unchanged in enflurane and isoflurane animals and decreased slightly, yet significantly, during dipyridamole. All variables remained unchanged in the control group. Thus, isoflurane and dipyridamole interfered with MBF autoregulation and increased myocardial oxygen delivery out of proportion to myocardial demands. The lack of simultaneous increase in tissue oxygen pressures may reflect occurance of functional shunting on a cardiac microvascular level. These results also suggest that coronary vasodilating agents may not necessarily be beneficial for oxygenation of the intact myocardium.*

Key Words: HEART: blood flow, myocardial. HEART: myocardial oxygenation. ANESTHETICS, VOLATILE: isoflurane, enflurane.

Blood flow to the healthy heart is largely independent of aortic pressure within the autoregulatory range of 60 to 120 mm Hg, but is closely related to metabolic demands, i.e. myocardial oxygen consumption (1). Coronary vasodilation by pharmacologic agents uncouples myocardial blood flow (MBF) from metabolic demands and abolishes autoregulation, resulting in a perfusion pressure dependence of MBF (1–3). The volatile anesthetics enflurane and isoflurane are coronary vasodilators (4,5). They increase the ratio between myocardial oxygen supply and consumption and hence decrease oxygen extraction and increase coronary-venous PO_2 (5–8).

As coronary-venous PO_2 is considered a reflection of mean myocardial tissue PO_2 (1,6,9), coronary vasodilators should improve myocardial tissue oxygenation. However, coronary vasodilation induced by adenosine (10,11) or dipyridamole (12,13) is not necessarily beneficial in the intact heart in terms of distribution of blood flow or tissue oxygenation. The effects of volatile anesthetics on the ischemic myocardium are discussed contoversally. In patients with coronary artery disease, isoflurane produced ECG ST-segment depression (14). In dogs with collateral dependent myocardium isoflurane produced a de-

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crease in collateral flow and a decrement in collateral zone contraction similar to adenosine (15). In contrast, in another study using a similar canine model with collateral dependent myocardium isoflurane, as well as halothane, did not effect collateral flow, nor did these anesthetics alter epicardial ECG ST-segments (16).

No data exist, however, about the effects of the volatile anesthetics on the actual oxygenation of the intact myocardium. We therefore investigated in a canine preparation with intact hearts and coronary circulation whether the increased ratio between myocardial oxygen delivery and consumption induced by isoflurane, enflurane and dipyridamole would result in a concomitant increase in myocardial tissue oxygenation.

Methods

Following approval by the animal investigation committee, 24 adult mongrel dogs with a mean body weight of 29 kg were anesthetized with intravenous ketamine (10 mg/kg), flunitrazepam (0.01 mg/kg) and atropine (0.5 mg). The long-acting narcotic piritramid ($1\ mg\cdot kg^{-1}\cdot h^{-1}$) and the muscle relaxant pancuronium bromide ($0.03\ mg\cdot kg^{-1}\cdot h^{-1}$) were infused throughout the study. Following tracheal intubation the animals were mechanically ventilated with a mixture of oxygen and N_2O (Servo Ventilator 900B, Siemens, Erlangen, West-Germany). The inspired oxygen fraction was adjusted to maintain arterial PO_2 at 100 mm Hg. At a respiratory rate of 15/min tidal volume was set to keep end-expiratory CO_2 at 4.5 vol%. End-expiratory pressure was +3 cm H_2O to avoid atelectasis and body temperature was kept constant by external heating.

A polyethylene catheter was placed in the abdominal aorta via a femoral artery. External jugular veins were used for placing a 7-French thermistor equipped catheter in the pulmonary artery and a 2.5-mm outer diameter tubing with side holes at its tip through the coronary sinus in the great cardiac vein. Correct position of the latter catheter was verified by fluoroscopy and, after thoracotomy, by digital palpation. Following a left side thoracotomy the pericardium was opened and a catheter inserted into the left atrium for measuring atrial pressures and for injecting radioactive microspheres. A highly flexible silicone rubber disc was fixed with 4-5 atraumatic sutures to the surface of the beating left ventricle to serve as an electrode holder for the O_2 sensitive multiwire electrode.

The reference withdrawal method was applied to measure blood flow to the myocardium with radioactive microspheres (17). We used standard carbonized microspheres with mean diameters of 15 ± 0.9 μm labelled with 141-Ce, or 95-Nb (3-M Company, St. Paul, MN). For each blood flow determination 2.5-4.0 million microspheres suspended in 0.9% saline were injected over 25–30 sec through the left atrial catheter which was subsequently flushed with 10 ml 37°C saline. Coronary-venous reference samples were withdrawn to detect shunting of microspheres through the cardiac microvasculature.

At the end of each experiment the dog was killed by iv KCl and the heart removed. Large vessels, valves and epicardial fat were removed and the heart dissected into 51 tissue specimens (left atrium, 2; right atrium, 2; right ventricle, 8; septum, 15; left ventricular free wall, 24). The free wall of the left ventricle was sliced into three transmural layers (subepicardial, mid, subendocardial). Radioactivity data obtained in a 1024 channel multiple regions of interest gammacounter (Model 9520, Packard Instruments, Downer's Grove, IL), were corrected for background and crossover activity. The total number of microspheres trapped and blood flow per g tissue were determined in each individual sample. Vascular resistance of the left ventricle was calculated as the quotient of the mean diastolic aortic to mean left atrial pressure difference and total left ventricular blood flow (LV + septum).

The method used herein to determine oxygen pressure fields has been described in detail (18,19). In brief, it consists of a Clark type electrode (20) with eight thin platinum cathodes and a Ag/AgCl anode. The electrode is covered with a Teflon membrane and placed on the surface of the left ventricle. At a constant polarization voltage of approximately −700 mV a single platinum wire (diameter 15 μm) registers a reduction current linearily dependent on the partial pressure of oxygen. The mean distance between 2 wires is 100 μm. The radius of the oxygen sensitive surface area of each single platinum wire depends on the thickness of the membrane and is 20 to 25 μm with the membrane of 25 μm used in the experiments (19).

The total weight of the PO_2-electrode is less than 1.5 g, thereby avoiding ischemia due to excessive pressure (19). Control experiments have shown that the electrode can be kept in place without changing its position for more than an hour without altering tissue PO_2. Pilot studies also demonstrated that there is no influence of oxygen from the ambient air, since suffusion of the electrode with pure oxygen or pure nitrogen had no effect on the resulting PO_2 values. Finally, correct contact of the electrode with the myocardial tissue was also verified after killing the animals by i.v. potassium-chloride, where all wires recorded values of zero mm Hg within 2 minutes. In 5 further experiments, which had been performed in pigs, animals were killed by slow infusion of KCN into the left atrium to inhibit cytochrome aa_3 and thus O_2 utilization. We observed an initial steep increase of myocardial tissue PO_2 (average +57%) within 1 minute and subsequently, after cardiac arrest had occurred, a slow decrease of tissue PO_2 to zero mm Hg over about 10 minutes.

The hemispheric catchment area of a single platinum wire (radius about 25 μm) of the electrode gives an averaged oxygen tension measurement from a tissue volume including several myocardial muscle cells, surrounding connective tissue, capillaries and smaller arterioles or venules. 80 to 100 single PO_2 values were determined in all experiments for each PO_2 recording to obtain representative distribution curves of tissue PO_2 (19,21–24).

Reduction current signals from each of the 8 channels were amplified, digitized and processed, using a PDP 11/23 computer (Digitial Equipment Corporation, Maynard, MS). The electrode was calibrated before and after reach recording using calibration gases with 0%, 5% and 10% oxygen in nitrogen. In vitro studies had demonstrated that the reduction current of the electrode wires increased linearly within this range when PO_2 was increased in steps of 1 vol%. Frequency distribution curves of 80 to 100 individual oxygen pressure measurements were obtained by turning the electrode several times in the holder. The results are presented both as mean values and as frequency distribution curves which give variabilities and distribution patterns of the PO_2 values. The PO_2 histograms then reflect tissue oxygenation, giving the net result of nutritive blood flow and tissue oxygen consumption (12,21).

Blood gas parameters in arterial, mixed-venous and coronary-venous blood samples were derived from a gas analyzer (Analysator D, Eschweiler & Co., Kiel, West-Germany). Hemoglobin concentrations, O_2-saturations and O_2-contents were derived from a CO-oxymeter (CO-oxymeter 282, Instrumentation Laboratory Inc., Lexington, MA). All determinations were corrected for temperature and performed in duplicate. Left ventricular oxygen delivery and uptake were calculated by arterial oxygen content times left ventricular blood flow and by the arterial to coronary-venous oxygen content difference times left ventricular flow, respectively.

At the end of the preparation period N_2O was discontinued and anesthesia maintained by i.v. piritramid. The animals were allowed to stabilize for 30 minutes. Baseline recordings of hemodynamic and blood gas parameters, myocardial surface PO_2 and myocardial blood flow were then made. Studies were performed in four groups of dogs. In the animals of the control group (n = 5) measurements were repeated after 60 minutes. The animals of group 2 received enflurane (n = 6; 1.1 vol%), animals of group 3 isoflurane (n = 8; 0.7 vol%) while piritramid infusion was continued at an unchanged rate. These concentrations were considered to be equianesthetic (25). Measurements were repeated after 60 minutes. End-expiratory anesthetic concentrations were measured using a multigas analyzer (EMMA, Engström Medical AB, Sweden). The EMMA sensor was separated from the animals' expired air by a humidity-retaining artificial nose (Edith, Engström). In the animals of the fourth group (n = 5) dipyridamole (0.4 mg/kg) was slowly injected. This amount decreased MAP to a degree similar to the decrease produced by enflurane and isoflurane. Thereafter, MAP was kept at this level by repeated injections of small amounts of dipyridamole and measurements were obtained after 20 minutes. Left atrial pressure was held constant during the time course of the experiments by infusion of crystalloid solutions.

Data on hemodynamic and blood gas variables are presented as means ± standard error of the mean (SEM). Myocardial PO_2 distribution curves are given as histograms with PO_2-classes of 5 mm Hg. Stastistically significant differences between baseline and the second experimental step were evaluated by Wilcoxon test. Differences between the four groups were evaluated by Kruskal Wallis analysis, followed by adequate multiple comparisons. A p-value < 0.05 was considered statistically significant.

Results

The results are summarized in the tables (1–4). No significant changes of hemodynamic variables, blood flow or tissue PO_2 were detected in the animals of the control group during the observation period of 60 minutes (Table 1).

Heart rate remained essentially unchanged in the enflurane (Table 2) and in the isoflurane (Table 3) animals, but increased significantly during dipyridamole (Table 4). Mean arterial pressure was reduced to 69 ± 6, 73 ± 4 and 67 ± 5 mm Hg in the enflurane, isoflurane and dipyridamole animals, respectively. Coronary perfusion pressure (estimated by mean diastolic aortic pressure minus mean left atrial pressure) decreased similarly in these three groups. No statistically significant differences were found between the three experimental groups. Cardiac output

Table 1. Control Group (n = 5; means ± SEM)

	Baseline	60 min
HR (min^{-1})	89 ± 6	81 ± 6
MAP (mm Hg)	90 ± 5	85 ± 4
CPP (mm Hg)	73 ± 7	71 ± 5
CO (ml·min^{-1}·kg−1)	137 ± 15	119 ± 8
LAP (mm Hg)	4.7 ± 0.9	4.7 ± 1.2
MPAP (mm Hg)	14.9 ± 0.7	15.1 ± 0.4
SVR (dyn·cm·sec^{-1})	1917 ± 262	2030 ± 175
a-PO$_2$ (mm Hg)	106 ± 4	110 ± 2
pH	7.36 ± 0.01	7.34 ± 0.01
c-PO$_2$ (mm Hg)	32.5 ± 1.3	33.5 ± 1.2
c-AVDO$_2$ (Vol%)	7.0 ± 1.2	6.7 ± 0.3
MBF (ml·min^{-1}·100g^{-1})	79 ± 10	80 ± 8
%CO (%)	3.1 ± 0.2	3.6 ± 0.3
CVR (mm Hg·min·g·ml^{-1})	97 ± 12	90 ± 8
endo/epi	0.95 ± 0.10	1.12 ± 0.14
D-O$_2$ (ml·min^{-1}·100g^{-1})	10.6 ± 1.4	10.8 ± 1.8
C-O$_2$ (ml·min^{-1}·100g^{-1})	5.6 ± 0.8	5.4 ± 0.4
D-O$_2$/C-O$_2$	1.9 ± 0.1	2.0 ± 0.1
P$_t$O$_2$ (mm Hg)	56 ± 3	60 ± 4

Abbreviations: HR, heart rate; MAP, mean arterial pressure; CPP, coronary perfusion pressure; CO, cardiac output; LAP, left atrial pressure; MPAP, mean pulmonary arterial pressure; SVR, systemic vascular resistance; V$_{max}$, maximal contractile element shortening; a-PO$_2$, PO$_2$ in arterial blood; pH, pH in arterial blood; c-PO$_2$, PO$_2$ in coronary-venous blood; c-AVDO$_2$, arterial to coronary-venous oxygen content difference; MBF, bloodflow to the myocardium of the left ventricle; %CO, fraction of cardiac output received by the myocardium of the left ventricle; CVR, coronary vascular resistance of the left ventricle; endo/epi, subendocardial to subepicardial blood flow ratio; D-O$_2$, oxygen delivery to the left ventricle; C-O$_2$, oxygen consumption of the left ventricle; D-O$_2$/C-O$_2$, myocardial oxygen delivery to consumption ratio; P$_t$O$_2$, myocardial surface tissue PO$_2$.

Table 2. Enflurane Group (n = 6; means ± SEM)

	Baseline	Enflurane
HR (min^{-1})	93 ± 3	86 ± 2^{d}
MAP (mm Hg)	100 ± 4	69 ± 6^{bc}
CPP (mm Hg)	89 ± 4	60 ± 7^{bc}
CO (ml·min^{-1}·kg^{-1})	136 ± 11	111 ± 14^{bdi}
LAP (mm Hg)	7.7 ± 0.9	7.4 ± 0.7
MPAP (mm Hg)	17.7 ± 0.6	15.0 ± 0.5
SVR (dyn·cm·sec^{-1})	1859 ± 198	1535 ± 101
a-PO$_2$ (mm Hg)	96 ± 4	96 ± 4
pH	7.39 ± 0.01	7.38 ± 0.02
c-PO$_2$ (mm Hg)	27.9 ± 0.9	29.6 ± 0.5^{d}
c-AVDO$_2$ (Vol%)	8.4 ± 0.5	7.1 ± 06^{bcd}
MBF (ml·min^{-1}·100g^{-1})	105 ± 7	86 ± 4^{cd}
%CO (%)	3.9 ± 0.1	4.3 ± 0.3^{d}
CVR (mm Hg·min·g·ml^{-1})	87 ± 9	71 ± 8^{bd}
endo/epi	0.99 ± 0.08	0.95 ± 0.04
D-O$_2$ (ml·min^{-1}·100g^{-1})	14.6 ± 1.3	10.7 ± 0.3^{bcd}
C-O$_2$ (ml·min^{-1}·100g^{-1})	8.7 ± 0.4	6.1 ± 0.4^{bcd}
D-O$_2$/C-O$_2$	1.7 ± 0.1	1.8 ± 0.2^{bd}
P$_t$O$_2$ (mm Hg)	61 ± 2	58 ± 2

Abbreviations as in table 1;
$^{b}p < 0.05$ vs baseline; $^{c}p < 0.05$ vs control group; $^{d}p < 0.05$ vs dipyridamole group; $^{i}p < 0.05$ vs isoflurane group.

Table 3. Isoflurane Group (n = 8; means ± SEM)

	Baseline	Isoflurane
HR (min^{-1})	93 ± 4	87 ± 5^{d}
MAP (mm Hg)	110 ± 4	73 ± 4^{bc}
CPP (mm Hg)	98 ± 4	61 ± 4^{bc}
CO (ml·min^{-1}·kg^{-1})	133 ± 13	117 ± 12^{bde}
LAP (mm Hg)	7.0 ± 0.9	7.0 ± 0.9
MPAP (mm Hg)	18.3 ± 1.6	16.1 ± 1.3
SVR (dyn·cm·sec^{-1})	2214 ± 158	1594 ± 63^{bcd}
a-PO$_2$ (mm Hg)	104 ± 1	104 ± 2
pH	7.38 ± 0.02	7.39 ± 0.02
c-PO$_2$ (mm Hg)	29.8 ± 1.1	36.5 ± 2.0^{bd}
c-AVDO$_2$ (Vol%)	9.3 ± 0.5	5.5 ± 0.5^{bc}
MBF (ml·min^{-1}·100g^{-1})	99 ± 11	119 ± 19^{d}
%CO (%)	4.4 ± 0.5	5.6 ± 0.9^{bd}
CVR (mm Hg·min·g·ml^{-1})	104 ± 8	62 ± 9^{bcd}
endo/epi	1.00 ± 0.04	1.01 ± 0.04
D-O$_2$ (ml·min^{-1}·100g^{-1})	15.4 ± 1.7	16.0 ± 2.5^{d}
C-O$_2$ (ml·min^{-1}·100g^{-1})	9.0 ± 0.8	6.2 ± 0.7^{bcd}
D-O$_2$/C-O$_2$	1.7 ± 0.1	2.5 ± 0.3^{bcd}
P$_t$O$_2$ (mm Hg)	65 ± 4	62 ± 4

Abbreviations as in table 1;
$^{b}p < 0.05$ vs baseline; $^{c}p < 0.05$ vs control group; $^{d}p < 0.05$ vs dipyridamole group; $^{e}p < 0.05$ vs enflurane group.

decreased 18% during enflurane and 12% during isoflurane, but increased 56% with dipyridamole. The reduction of systemic vascular resistance by 17% with enflurane, by 28% with isoflurane and by 59% with dipyriamole reflects the peripheral vasodilating potencies of these drugs.

Myocardial blood flow decreased 18% with enflurane, but increased 20%, yet not significantly, with isoflurane. Additionally, MBF increased 304% with dipyridamole. The fraction of cardiac output to the left ventricle remained essentially unchanged with enflurane, but increased significantly with isoflurane and dipyridamole. Coronary vascular resistance (CVR) decreased significantly 18% with enflurane, 40% with isoflurane and 83% with dipyridamole. The subendocardial to subepicardial blood flow ratios remained essentially unchanged in the animals of all groups, i.e., none of the drugs caused a transmural redistribution of myocardial blood flow. No microspheres were detected in the coronary-venous reference samples. Left and right renal cortical flow values did not differ by more than 10%, indicating homogeneous mixing of microspheres with blood.

There was no significant change in the myocardial oxygen balance in the control animals. The ratio between myocardial oxygen delivery and consumption increased significantly 6% with enflurane, 47% with isoflurane and 380% with dipyridamole. The 6% and the 47% increases in the anesthetic groups are not statistically different from each other, but both are significantly lower than the 360% increase with dipyridamole. These changes were followed by a significant increase of coronary-venous PO$_2$, only with isoflurane and dipyridamole. The arterial to coro-

Table 4. Dipyridamole Group (n = 5; means ± SEM)

	Baseline	Dipyridamole
HR (min^{-1})	93 ± 13	122 ± 16^{bcei}
MAP (mm Hg)	95 ± 5	67 ± 5^{bc}
CPP (mm Hg)	79 ± 5	56 ± 5^{bc}
CO ($ml \cdot min^{-1} \cdot kg^{-1}$)	121 ± 8	189 ± 13^{bcei}
LAP (mm Hg)	5.5 ± 0.6	4.9 ± 0.8
MPAP (mm Hg)	16.6 ± 0.6	15.0 ± 0.9
SVR ($dyn \cdot cm \cdot sec^{-1}$)	2328 ± 262	953 ± 59^{bcei}
a-PO_2 (mm Hg)	113 ± 4	111 ± 7
pH	7.35 ± 0.01	7.35 ± 0.02
c-PO_2 (mm Hg)	33.2 ± 1.3	55.8 ± 3.0^{bcei}
c-$AVDO_2$ (Vol%)	6.6 ± 0.3	1.9 ± 0.3^{bcei}
MBF ($ml \cdot min^{-1} \cdot 100g^{-1}$)	100 ± 11	404 ± 44^{bcei}
%CO (%)	3.3 ± 0.3	8.8 ± 1.3^{bcei}
CVR ($mm\ Hg \cdot min \cdot g \cdot ml^{-1}$)	84 ± 12	14 ± 1.1^{bcei}
endo/epi	1.15 ± 0.14	1.07 ± 0.11
D-O_2 ($ml \cdot min^{-1} \cdot 100g^{-1}$)	13.3 ± 2.0	50.8 ± 7.4^{bcei}
C-O_2 ($ml \cdot min^{-1} \cdot 100g^{-1}$)	6.4 ± 0.6	7.5 ± 1.4^{ei}
D-O_2/CO_2	2.0 ± 0.1	7.6 ± 0.2^{bcei}
P_tO_2 (mm Hg)	61 ± 5	55 ± 5^{bc}

Abbreviations see table 1;
$^b p < 0.05$ vs baseline; $^c p < 0.05$ vs control group; $^e p < 0.05$ vs enflurane group; $^i p < 0.05$ vs isoflurane group.

nary-venous oxygen content difference decreased in all three groups.

In contrast to coronary-venous PO_2, myocardial surface tissue PO_2 of the enflurane and isoflurane animals remained unchanged. If all individual PO_2 values are considered, these ranged from 40 to 85 mm Hg with a mean of 61 mm Hg during baseline and from 40 to 80 mm Hg with a mean of 58 mm Hg during Enflurane (Fig. 1). In the isoflurane animals individual baseline PO_2 values ranged from 35 to 90 mm Hg with a mean of 65 mm Hg. During isoflurane the range of PO_2 values was unchanged, the mean PO_2 value of 62 mm Hg almost identical with the baseline value (Fig. 2). In the dipyridamole animals mean myocardial surface tissue PO_2 decreased significantly from 61 to 55 mm Hg. The range of the summary PO_2 histograms, however, was unchanged at 25 to 80 mm Hg before and during dipyridamole (Fig. 2).

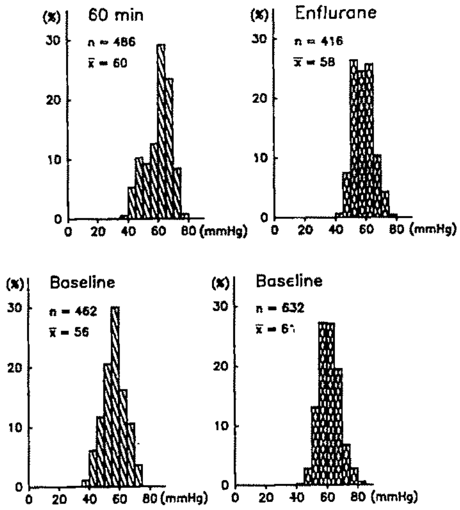

Figure 1. Oxygen pressure distribution curves from the surface of the left ventricle of control and enflurane animals at baseline (bottom), after 60 min basal anesthesia (top left) and during enflurane (top right). The total numbers of PO_2 values (n) and the mean oxygen pressures (x) are given.

Discussion

The present study was carried out in dogs under basal anesthesia with the long-acting narcotic piritramid. This was necessary because of the surgical preparation required for the PO_2 determinations on the surface of the beating heart. The control animals, which received no coronary vasodilator, allowed assessment both, of time dependent alterations in the preparation, as well as of disappearing effects of the drugs given for induction of anesthesia. In this group all parameters remained stable over the one hour observation period. When interpreting the data of this study, it should be kept in mind that the drugs given for induction and maintenance of anesthesia might have influenced the results by interacting with the tested drugs (26,27). However, basal anesthesia was identical for all groups.

Blood flow to the heart was determined by radioactive microsphere method using a reference sample technique (17). Particles were injected into the left atrium to guarantee homogenous mixing with blood already at the aortic root (28). Homogenous mixing was verified by comparing the left and right renal cortical flow values which did not differ by more than 10%. Mean diameter of the microspheres used was 15 μm. With this size distribution of the streaming microspheres is not significantly different from red blood cells (29). We injected 2.5–4.0 million microspheres to be sure that all tissue specimens contained at least 400 microspheres. In this study the numbers of microspheres per myocardial tissue sample actually varied between 1000 and 2000, providing a distribution variability of ±5% at the 95% confidence level (28).

The technique applied for measuring surface PO_2 provides the advantage of atraumatic measurements of local tissue oxygenation (in contrast to needle electrodes, which may produce trauma and hemorrhage in the tissue, thereby disturbing microcirculation). Additionally, the covering Teflon membrane of the surface electrode avoids contamination of the platinum wires with biologic material, which may subsequently be reduced by the voltage of the elec-

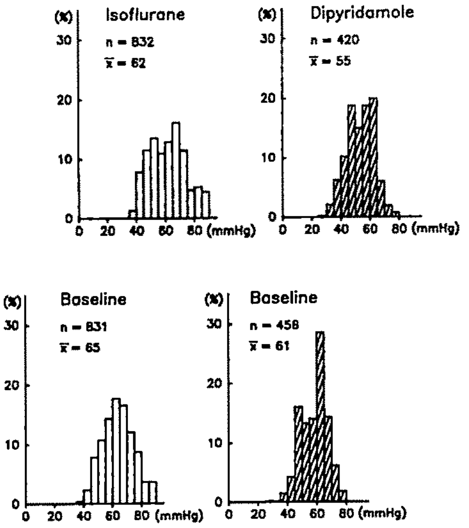

Figure 2. Oxygen pressure distribution curves from the surface of the left ventricle of isoflurane and dipyridamole animals at baseline (bottom), during isoflurane (top left) and during dipyridamole (top right). The total numbers of PO$_2$ values (n) and the mean oxygen pressures (x) are given.

trode. This contamination of the electrode would alter PO$_2$ determinations and lead to a considerable electrode drift (20).

PO$_2$ measurements on organ surfaces do not necessarily reflect oxygen tensions in deeper layers of tissue. Measurements of transmural myocardial oxygen tensions with needle electrodes suggest a lower tissue PO$_2$ in the subendocardium compared to the subepicardium (12,30). The data obtained by means of a surface electrode, therefore, do certainly not describe subendocardial tissue oxygenation. However, results obtained by means of needle electrodes (12,31,32) also suggest that transmural changes of myocardial tissue PO$_2$ can be predicted by measuring epicardial PO$_2$.

Since the catchment area of the surface electrode includes several myocardial muscle cells, connective tissue and small vessels, the electrode does not measure intracellular but rather extracellular oxygen tensions (12). In working and in resting skeletal muscle intracellular oxygen tensions have been shown to be rather low, 5 to 10 mm Hg (33) and 1 to 3 mm Hg (34,35). Using identical equipment as in our study, skeletal muscle surface PO$_2$ values ranged from 0 to 70 mm Hg with mean surface oxygen tensions between 12 and 35 mm Hg (21,36,37). The difference between intracellular PO$_2$ values and polarographically obtained tissue PO$_2$ by surface electrodes might result from the fact that oxygen is measured in different tissue compartments, that is, intracellular versus extracellular PO$_2$. The physiological mechanisms reponsible for this gradient between extracellular and intracellular PO$_2$ are not yet understood, however. We applied the method of measuring PO$_2$ by means of a surface electrode, since it instantly and reproducibly detects tissue oxygenation without major trauma and because it has proved useful in many experimental approaches on different tissues such as skeletal muscle (21,36,37), skin (24), brain (22), liver (38,39) and myocardium (40).

As coronary vasodilation abolishes, or at least interferes with autoregulation in the coronary vascular bed and results in a closer relationship between coronary flow and perfusion pressure (3), it is important to note that the concentrations of enflurane, isoflurane and dipyridamole applied in the present study resulted in comparable mean arterial pressures of about 70 mm Hg and in comparable coronary perfusion pressures of 56 to 61 mm Hg. The general influences of the vasodilators enflurane, isoflurane and dipyridamole on systemic hemodynamic parameters agree with data from literature (6,13,41,42,43). In accordance with previous studies, coronary vasodilation was only slight with enflurane (6,44), more pronounced with isoflurane (4,6,7) and most potent with dipyridamole (12,13,43,45). Myocardial blood flow exceeded metabolic demands especially with isoflurane and dipyridamole as it is indicated by significant increases in coronary venous PO$_2$ and decreases in oxygen extraction. Some authors suggested a transmural redistribution of myocardial blood flow with the coronary dilators dipyridamole and adenosine with either an increase (46) or a decrease of endocardial to epicardial blood flow ratio (10,12). In the present study, like in most others, the unchanged endo/epi ratio excluded a transmural redistribution of myocardial blood flow with enflurane, isoflurane or dipyridamole (4,11,45,47,48).

The baseline values of myocardial O$_2$ consumption as well as O$_2$ delivery were somewhat higher in the enflurane and isoflurane groups as compared to the control and didyridamole groups. Thus there were no major differences in the ratios between O$_2$ delivery and O$_2$ consumption between the four groups and the influence of these differences on the results during coronary vasodilation should be neglegible. In agreement with data from literature (6,14,44), we observed a marked reduction of myocardial O$_2$ consumption with both anesthetics. This is ascribed to the negative inotropic effects of the volatile anesthetics. Myocardial blood flow was slightly reduced with enflurane and well maintained with isoflurane. Thus the ratio between oxygen delivery and consumption increased only slightly with enflurane and markedly, yet, not statistically different from enflurane, with isoflurane. Dipyridamole slightly increased O$_2$ consumption, largely by increasing heart rate, but, by a

304% increase of blood flow, caused a shift of myocardial oxygen balance, significantly increasing the ratio between oxygen delivery and consumption by 280%. In agreement with other studies the improvement of the oxygen balance resulted in an increase of coronary venous PO_2 and a decrease of myocardial oxygen extraction in the enflurane and isoflurane (5,6,44), as well as in the dipyridamole (11–13) groups. From both the increased coronary venous PO_2 and the improvement of the oxygen balance one would expect an improvement of myocardial tissue oxygenation, i.e. an increase in myocardial tissue PO_2 (1,9). However, the tissue PO_2 values on the surface of the left ventricle remained essentially unchanged in enflurane and isoflurane groups and even decreased slightly, but significantly, in the dipyridamole animals. These observations could be explained by a redistribution of blood flow from outer to inner layers of the left ventricular myocardium. However, as mentioned above, unchanged endo/epi ratios suggest that there was no such redistribution.

Another explanation seems more likely: A sizeable fraction of myocardial blood flow passed the myocardial vascular bed without delivering oxygen to the tissue, i.e. shunt perfusion occurred during coronary vasodilation. Since no 15 μm microspheres were detected in the coronary-venous reference samples, shunt perfusion must have occurred in vessels smaller than 15 μm, i.e. in capillaries.

As, to the best of our knowledge, no data have been published concerning myocardial capillary flow distribution during vasodilation, the results of the present study will be related to results obtained in skeletal muscle. This seems justified by the recent work of Potter and Groom (49) who analyzed the capillary networks of heart and skeletal muscle. The authors found both the myocardial and the skeletal muscle capillary networks to be parallel in nature and to follow the arrangement of the muscle fibers. Capillary diameters ranged between 2 and 10 μm in both tissues and showed almost identical diameter distribution patterns.

Functional shunting in skeletal muscle has been described previously (50–54). Administration of acetylcholine or beta-adrenergic stimulation caused a decrease of tissue PO_2 despite a concomitant increase of perfusion or venous PO_2, thus indicating a considerable increase of functional tissue shunt (52,53).

As early as 1966 Renkin et al. (54) explained functional shunting through vessels by a reduced blood flow through capillary pathways of higher resistance (longer capilliaries with greater surface areas) and an increased blood flow through the shorter capillary pathways with a low intrinsic resistance. This model is consistent with the data of the present study, suggesting that the increase of total myocardial blood flow during coronary vasodilation was mainly due to an increase of flow in the low resistance capillaries (i.e. short capillary pathways).

It remains unclear whether the coronary vasodilators investigated in this study impair capillary flow distribution by directly relaxing precapillary sphincters of short capillaries (54). Heterogeneity in capillary flow might also result from a decreased perfusion pressure with passive redistribution of flow from longer nutritional capillaries to short non-nutritional capillaries (51).

Another explanation for the discrepancy between myocardial oxygen balance and tissue PO_2 would be an increase of diffusional shunting of oxygen during coronary vasodilation. This type of arterial-venous shunting exists in canine myocardium for the inert gas hydrogen (55). Histologic analyses of the microvasculature of the dog left ventricular myocardium (56), however, suggest that diffusional shunting of oxygen should be negligible. Also, van Beck and Elzinga (57) showed that diffusional shunting of oxygen is negligible in the myocardial circulation.

The biologic or clinical significance of this shunt perfusion in intact hearts, with a separation of myocardial blood flow into a nutritive and a non-nutritive fraction during coronary vasodilation is not yet clear. The unchanged mean values of the PO_2 distribution curves with the less potent coronary vasodilators enflurane and isoflurane suggest that tissue oxygenation is not compromized under the experimental conditions of this study. A slight, but significant decrease of myocardial tissue PO_2 values in the dipyridamole animals indicates that despite the 300% increase of myocardial blood flow the nutritive fraction of capillary flow might be decreased. However, the unchanged range of the PO_2 values during dipyridamole and especially the fact that no leftward shift of the lowest PO_2 values occurred, seem to indicate that myocardial tissue oxygenation is not critically impaired.

Data of this study can be extrapolated to humans only with great caution. While coronary vasodilation induced by enflurane, isoflurane or dipyridamole seems to cause no danger in patients with intact coronary circulation, the significance of capillary shunt perfusion for patients with coronary artery disease remains unclear. Further experiments with animal models of coronary artery stenosis are necessary to gain more information on this problem.

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The Effect of Cimetidine and Ranitidine on the Duration of Action of Succinylcholine

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A recent study suggested that cimetidine prolongs the duration of action of succinylcholine (SCh). We examined this reported interaction, and investigated whether it is the result of inhibition of plasma cholinesterase (PChE). We also studied the effect of ranitidine on the duration of action of succinylcholine. Thirty patients were randomly assigned to three groups to receive oral cimetidine 300 mg or ranitidine 150 mg or no H_2-antagonist the night before surgery and again 1–2 hours prior to induction of anesthesia. Succinylcholine (1.5 mg/kg i.v.) was given to facilitate tracheal intubation after induction of anesthesia; neuromuscular function was monitored by evoked compound electromyogram. Pretreatment blood samples were analyzed for PChE activity. PChE activity and levels of appropriate H_2-antagonists were measured in preinduction blood samples. No significant effect of either cimetidine or ranitidine on the duration of action of SCh or PChE activity was demonstrated. We conclude that H_2-antagonists administered preoperatively do not prolong the duration of action of succinylcholine or alter PChE activity.

Key Words: NEUROMUSCULAR RELAXANTS—succinylcholine. PHARMACOLOGY—cimetidine, ranitidine. ENZYMES—plasma cholinesterase.

The H_2-receptor antagonists cimetidine and ranitidine are commonly prescribed for the treatment of peptic ulcer disease and to reduce the volume and acidity of gastric contents preoperatively. A recent study (1) showed that cimetidine administered preoperatively approximately doubled the duration of action of succinylcholine (SCh). Our clinical experience, however, has not suggested this effect. The current study was undertaken to further evaluate this reported interaction, and to determine if its mechanism is inhibition of plasma cholinesterase (PChE). In addition, we examined the effect of ranitidine on the duration of action of SCh.

Methods

We studied thirty adult ASA class I-II patients with a mean age of 44.6 yr ± 15.5 SD (range 24–70 yr) scheduled for elective surgical procedures. Approval of the Human Subjects Protection Committees at our institutions and informed consent were obtained. No patient had a known neuromuscular disorder. All patients received midazolam 0.03–0.06 mg/kg i.v. in the preoperative room. Anesthesia was induced with fentanyl 1–2 μg/kg and thiamylal 5 mg/kg i.v. Succinylcholine 1.5 mg/kg IV was administered to facilitate tracheal intubation, and anesthesia was maintained with 70% nitrous oxide in oxygen and isoflurane (0.75–1.25 inspired concentration). After induction of anesthesia and prior to the administration of SCh, the ulnar nerve was stimulated supramaximally with repetitive trains-of-four (2 Hz at 20 sec intervals). and the baseline evoked compound electromyogram of the adductor pollicus muscle was obtained using a Puritan-Bennett Datex NMT monitor. The duration of action of SCh was defined as spontaneous recovery from onset of complete twitch depression to 50% of baseline twitch height.

Patients were randomly assigned to one of three groups (n = 10 each). Group I patients received no H_2-antagonist. Group II patients received oral cimetidine 300 mg the night before surgery and 1–2 hours

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Table 1. Effect of Cimetidine and Ranitidine on Duration of Action (min) of Succinylcholine 1.5 mg/kg i.v.

	Group I (Control) n = 10	Group II (Cimetidine) n = 10	Group III (Ranitidine) n = 10
	12	12	10
	7	8	10
	12	12	7
	8	8	13
	7	16	9
	15	13	10
	11	13	9
	14	12	11
	12	13	13
	12	8	16
Mean ± SD =	11.0 ± 2.79	11.3 ± 2.63	10.8 ± 2.57

No significant difference between the groups, unpaired *t*-test. Duration of action = time from onset of complete twitch depression to 50% twitch recovery.

prior to induction. Group III patients received oral ranitidine 150 mg according to the same schedule. Blood samples for measurement of PChE activity were drawn before the first dose of cimetidine or ranitidine in Groups II and III and immediately prior to induction in all patients. In Groups II and III, the second blood sample was also analyzed for cimetidine and ranitidine levels.

Enzyme Determination

Plasma cholinesterase activities were measured spectrophotometrically with benzoylcholine as a substrate according to the technique described by Kalow and Lindsay (2). Quality control analysis in our laboratory with this technique produced values with a standard deviation of 8 activity units.

Ranitidine Assay

Plasma was removed from venous blood samples and frozen until analysis. Ranitidine hydrochloride was measured using a liquid chromatographic method described by Carey et al. (3). All samples were analyzed three times with a reproducibility of 10%.

Cimetidine Assay

Whole blood samples were kept frozen after collection until analyzed by the method of Randolph et al., with a reproducibility for assay values of 10% (4).

Analysis of the data obtained was performed using the Student's *t*-test, and analysis of covariance, assuming $P < 0.05$ represents statistical significance.

Results

The results are summarized in Tables 1 and 2. There was no significant difference in duration of SCh neuromuscular block between the cimetidine, ranitidine and control groups. In addition, we found no significant difference in PChE activity after administration of cimetidine or ranitidine. No significant correlation between drug levels and duration of action of SCh was noted. In patients treated with cimetidine, nine of 10 had whole blood cimetidine levels within the therapeutic range, and one had a subtherapeutic level (mean = 1.6 μg/ml, SD = 0.85). In patients treated with ranitidine, 8 of 10 had plasma ranitidine levels within the therapeutic range, and two had subtherapeutic levels (mean = 182 ng/ml, SD = 99).

Table 2. Effect of Cimetidine and Ranitidine on PChE Activity

Group I (Control) n = 10	Group II (Cimetidine) n = 10		Group III (Ranitidine) n = 10	
PChE	Pre-PChE	Post-PChE	Pre-PCh	Post-PChE
112	82	65	140	137
138	59	59	119	118
127	120	145	138	129
84	140	121	146	146
158	109	101	192	167
107	98	89	68	52
94	70	54	109	106
137	48	44	88	74
166	62	53	104	105
114	145	120	63	69
Mean ± SD = 124 ± 27	93 ± 34	85 ± 35	117 ± 39	110 ± 35

PChE activity normal range = 40–120 U. No significant difference in PChE activity between pre- and post- treatment with cimetidine or ranitidine, paired t-test.

Discussion

It has been reported that in patients treated with cimetidine preoperatively, the duration of SCh-induced neuromuscular block is approximately doubled (1). The duration of action of SCh depends primarily on its hydrolysis by PChE. Kambam et al. (1) suggested PChE inhibition may have been responsible for the effect of cimetidine on the duration of action of SCh. Recently, several in vitro studies have shown that PChE activity is inhibited by cimetidine only at whole blood levels greater than 50 times therapeutic (5,6,7). In vivo, cimetidine administered to patients preoperatively has no inhibitory effect on PChE activity (6). In vitro, the median inhibitory concentration of ranitidine for inhibition of PChE is 25 times the therapeutic plasma level (8). The effect of ranitidine administration on PChE activity in patients has not been investigated.

Our results showed no difference in duration of action of SCh in patients treated with either cimetidine or ranitidine compared to those not given a H_2-antagonist. Stirt et al. (9) also showed no difference in duration of SCh-induced neuromuscular block between cimetidine treated and control groups. Our data confirmed that of Kambam et al. (6) showing no decrease in PChE activity in patients given cimetidine preoperatively. In addition, we found that no decrease in PChE activity resulted from preoperative ranitidine administration.

Several in vitro and in vivo animal studies have shown that cimetidine or ranitidine alone in much higher concentrations than those obtained in the clinical setting may produce neuromuscular blockade, possibly due to ion channel block (7). In view of our study and that of Stirt et al. (9), any interaction seems to be of no clinical importance.

There are few differences in protocol between our study and that of Kambam et al., (1) in which prolongation of SCh-induced neuromuscular blockade was reported after cimetidine administration. However, in their study, metaclopramide was also administered to many patients in an uncontrolled manner (personal communication). Kambam et al., have since reported that metaclopramide has a significant inhibitory effect on PChE activity and may prolong neuromuscular blockade due to succinylcholine (10). This may account for the differences in the results obtained in our study and those of Kambam's original study.

We found that H_2-antagonists at therapeutic blood levels had no significant effect on the duration of SCh-induced neuromuscular block. The preoperative administration of H_2-antagonists did not effect PChE activity. We believe that in clinical practice H_2-antagonists may be given preoperatively without concern for prolonging the duration of action of SCh.

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Bunegin-Albin Catheter Improves Air Retrieval and Resuscitation from Lethal Venous Air Embolism in Upright Dogs

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COLLEY PS, ARTRU AA. Bunegin-Albin Catheter improves air retrieval and resuscitation from letha l venous air embolism in upright dogs. Anesth Analg 1989;68:298–301.

Three types of catheters, the Arrow® multi-orifice catheter, the American Edwards 7 Fr Swan-Ganz® catheter and the Cook® Bunegin-Albin multi-orifice CVP catheter were evaluated for their ability to retrieve venous air emboli and effect on the success rate of resuscitation from venous air emboli. The catheters were inserted in dogs anesthetized with isoflurane (1.7%, inspired) and N_2O (66%) in O_2 and placed in the sitting position with the head 90° to the horizontal. Swan-Ganz® catheters were positioned with the right atrial (RA) port just above the junction of the superior vena cava (SVC) and the RA and the pulmonary artery (PA) port in the pulmonary artery. The Arrow® and Bunegin-Albin multi-orifice catheters were placed with the proximal orifice just above the SVC-RA junction and the distal orifice near the mid-RA. Dogs were then given a predetermined lethal dose of air (5 ml · kg^{-1}) over 30 sec via the jugular vein. Attempts to aspirate venous air emboli were begun with the first decrease in expired CO_2. Both RA and PA ports of the Swan-Ganz® catheter were used for aspiration. The amounts of gas retrieved expressed as a percent of the injected air and the incidence of successful resuscitation were compared. Significantly greater percentages of injected venous air were retrieved with the Bunegin-Albin catheter (63 ± 14%, mean ± SEM) than with the Arrow® multi-orifice catheter (6 ± 2%) or the Swan-Ganz® catheter (14 ± 5%). The success rate of resuscitation was significantly greater with the Bunegin-Albin catheter (4 of 6 dogs) than with either the Arrow® catheter or the Swan-Ganz® catheter , (1 of 6 in both groups). The Cook ® Bunegin-Albin multi-orifice catheter appears to be superior to the Arrow® multi-orifice catheter or the Swan-Ganz® catheter for aspiration of venous air in dogs placed in the sitting position.

Key Words: EMBOLISM, air.

We previously reported the results of a study in which we compared in dogs the usefulness of different types of right atrial (RA) catheters for aspiration of venous air emboli (VAE) (1). In that study, we examined the Cook® Bunegin-Albin multi-orifice catheter, the single orifice Sorenson® catheter and the RA port of a 7 F American Edwards Swan-Ganz® catheter. The Bunegin-Albin catheter was superior both in its ability to retrieve greater amounts of injected air and in the number of dogs that were successfully resuscitated. In that study, the dogs were in the prone, horizontal position and air was injected into the femoral vein. The experimental model, therefore, resembled clinical situations similar to those seen in patients undergoing cesarean section or other abdominal or pelvic procedures that have been reported to be associated with venous air embolism (2–3).

In the present study, we placed the dogs in the sitting position, with the head 90° to the horizontal and injected air into the jugular vein. This more closely resembles the situation that exists during a craniotomy with the patient in the sitting position. In addition, we examined an Arrow® multi-orifice catheter and both the RA and pulmonary artery (PA) ports of a Swan-Ganz® catheter comparing them to the Bunegin-Albin catheter. After determining the dose of venous air that is lethal to dogs, the catheters were evaluated for (1) percentage of injected venous air retrieved, and (2) success rate of resuscitation when air aspiration was the only method of treatment.

Methods

The experimental protocol was nearly identical to that

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outlined in our previous study of dogs in the prone, horizontal position (1). The study was approved by the Institutional Review Board. Thirty dogs (weight range = 14–22 kg) were anesthetized with isoflurane (1.7%, inspired) and N_2O (66%) in O_2. The dogs were ventilated to maintain PaO2 > 120 mm Hg and $PaCO_2$ at 35–40 mm Hg. Expired CO_2 was continuously monitored using a Beckman LB-2 medical gas analyzer. An electronic offset was used to minimize interference by expired N_2O on the strip chart recorder display. A femoral vein was cannulated for fluid administration and a second catheter was inserted into the left jugular vein for injection of air. A femoral artery was cannulated for sampling of blood for gas analysis and for continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Temperature was monitored by a nasopharyngeal thermistor probe and maintained at 37.0 ± 0.5°C by heat lamps or ice packs. Vascular volume was maintained by continuous saline infusion 4–6 $ml \cdot kg^{-1} \cdot min^{-1}$.

At the conclusion of the surgical preparation, wound edges were infiltrated with bupivacaine (0.5%) and the concentration of isoflurane was decreased to 0.5% (inspired, % N_2O unchanged). The dogs were placed in the sitting position, i.e. head and upper torso 90° to the horizontal, with the head fixed in a stereotaxic frame and lower torso and legs resting on the seat of a chair. Up to 200 ml of saline was given to achieve a central venous pressure (CVP) of approximately 2 mm Hg with the transducer zeroed at the top of the atrium. Once systemic variables had stabilized (25 min after decreasing isoflurane to 0.5%), baseline values for systemic variables were recorded. These included CVP or RA pressure, pulmonary capillary wedge pressure (PCWP), MAP, heart rate (HR), arterial blood gas tensions, arterial blood hemoglobin levels, and nasopharyngeal temperature.

To determine the fatal VAE dose in upright dogs, 6 of the 30 dogs were given venous air emboli of 3 $ml \cdot kg^{-1}$ over 20 sec, then 5 $ml \cdot kg^{-1}$ over 30 sec if they survived the initial dose, then 7 $ml \cdot kg^{-1}$ over 40 sec if they survived the 5 $ml \cdot kg^{-1}$ dose. At least 25 min were allowed between doses to permit cardiovascular re-stabilization. We found that the fatal VAE dose was 3 $ml \cdot kg^{-1}$ in 1 dog, 5 $ml \cdot kg^{-1}$ in 4 dogs and 7 $ml \cdot kg^{-1}$ in the remaining dog. Thus a dose of 5 $ml \cdot kg^{-1}$ was selected as the mean fatal VAE for the studies of air retrieval and resuscitation in the remaining 24 dogs. These 24 dogs were randomly assigned to one of four groups. Six of the dogs acted as controls and had no catheters inserted for aspiration of air. Six dogs had the Cook® Bunegin-Albin catheter inserted into the right jugular vein, 6 dogs had an American Edwards 7F Swan-Ganz® pulmonary artery catheter inserted and 6 dogs had an Arrow® Antecubital Central Venous Catheter inserted.

The Bunegin-Albin catheter is 61 cm long and has 1 distal orifice and 6 round side orifices, each 1.0 mm in diameter, with the most proximal orifice placed about 5 cm from the catheter tip. The Arrow® catheter is 100 cm long and has 1 distal orifice and 4 ovalshaped side orifices, each 1.0 × 1.5 mm in diameter, with the most proximal orifice placed about 3 cm from the tip. The Swan-Ganz® catheter is 110 cm long with the RA port 94 cm from the hub. The RA port is 0.5 mm in diameter and the distal PA port 2.2 mm × 0.5 mm in diameter. As in our previous study, the Bunegin-Albin and Arrow® catheters and RA port of the Swan-Ganz® catheter were examined in the position reported by Bunegin et al. (4) as optimum for aspirating air: with the proximal orifice near the SVC-RA junction and distal orifice near the mid-RA for the Bunegin-Albin and Arrow® multi-orifice catheters and the RA port of the Swan-Ganz® near the SVC-RA junction. The PA port of the Swan-Ganz® catheter was placed in the pulmonary artery. Catheters were positioned by using the catheter as an exploring EKG lead (5) and, for the Swan-Ganz® catheter, using the pulmonary artery pressure trace to confirm placement of the PA port in the pulmonary artery.

The RA port of the Swan-Ganz® catheter was advanced until the point of maximal negative P-wave deflection with no positive P-wave component. This point was taken to indicate that the port was at the SVC-RA junction. The RA port of the Swan-Ganz® catheter was then withdrawn approximately 1–2 cm above this point. The Bunegin-Albin catheter and the Arrow® catheter were advanced 1–2 cm once the point of maximum P wave deflection was reached. Since the proximal orifice and tip are about 3 and 5 cm apart, (Arrow® and Cook® catheters respectively) this maneuver placed the proximal port approximately 1 cm above the SVC-RA junction and the distal port in the mid-RA (5).

Resuscitation was attempted in all dogs with catheters. The only method of resuscitation used was aspiration of venous air emboli. Attempts to aspirate were made using 50 ml syringes attached to the catheter. One syringe was used with each of the catheters except that two syringes (one for the RA port and one for the PA port) were used with the Swan-Ganz® catheter. Aspiration was begun as soon as expired CO_2 decreased following injection of air with the Swan-Ganz® catheter. Both syringes were simultaneously used for aspiration. The "plunger" of

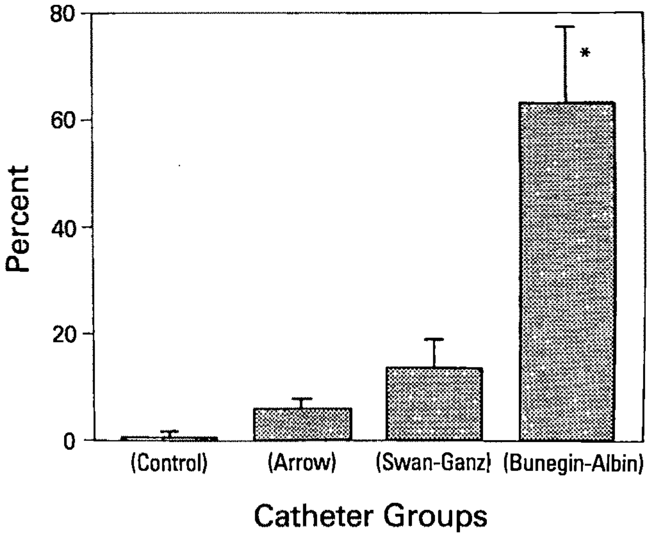

Figure 1. Amount of gas retrieved expressed as a percent of air injected. Values shown are means ± SEM. The percent retrieved was significantly greater ($p < 0.05$) with the Bunegin-Albin catheter than with the RA and PA ports of the Swan-Ganz® catheter or the Arrow® catheter.

Table 2. Catheter Resistances

Catheter	Resistance (cm $H_2O \cdot ml^{-1} \cdot min$)
Bunegin-Albin	0.77
Arrow®	5.75
Swan-Ganz®	
RA Port	8.70
PA Port	10.20

the 50 ml syringes was pulled back manually with as much force as could be generated by hand. The negative force generated during aspiration was not measured. Aspiration was continued until gas no longer was seen to be entering the syringes. In cases where large amounts of gas were retrieved, it was often necessary to use more than one 50 ml syringe. Invariably, blood was aspirated but because the amount of blood was small (10–40 ml) and was not significantly different between groups, no attempt was made to reinfuse the aspirated blood.

The volume of gas retrieved was expressed as a percent of injected air. The term "gas" is used as the retrieved gas was composed of both the injected air and whatever amount of nitrous oxide might have diffused into the injected air. This percent and systemic variables were compared between groups using analysis of variance. The incidence of successful resuscitation in different groups and the percentage of VAE that was retrieved in survivors and non-survivors were compared using the variance ratio test (6). A P value <0.05 was considered statistically significant. Resistance of the catheters was determined by measuring the flow of H_2O at 10, 20 and 30 cm H_2O pressure for 1–2 min and expressing resistance as cm $H_2O \cdot ml^{-1} \cdot min$.

Results

There were no differences between groups with respect to CVP or RA pressure, MAP, HR, temperature, PaO_2, $PaCO_2$, or arterial blood pH, bicarbonate and hemoglobin (not tabulated) prior to infusion of air.

A significantly greater amount of gas as a percent of the 5 $ml \cdot kg^{-1}$ air embolism dose was retrieved using the Bunegin-Albin catheter (63 ± 14%) (mean ± SEM) than with either the Swan-Ganz® RA and PA port (14 ± 5%), or the Arrow® catheter (6 ± 2%). (Fig. 1). The incidence of successful resuscitation from venous air embolism also was significantly higher using the Bunegin-Albin catheter (4 of 6 dogs) than with either the Swan-Ganz® catheter or Arrow® catheter groups (1 of 6 in both groups). The resistances of these catheters are shown in the Table. The percent of VAE dose retrieved in survivors ((62 ± 13%, n = 6) was significantly greater than the percent of VAE dose retrieved in non-survivors (10 ± 3%, n = 12, catheter groups only).

Discussion

In this study the mean fatal VAE dose was (5 $ml \cdot kg^{-1}$) in upright dogs given saline to achieve a CVP of approximately 2 mm Hg. This mean fatal VAE dose is similar to that reported in our previous study in dogs in the prone, horizontal position that were not given a saline load (1). The experimental model used by us in this study more closely resembles the situation that exists during a craniotomy with the patient in the sitting position than that represented by the prone dogs used in our previous study. Our results support our previously reported findings in prone dogs that the choice of venous catheter may have clinical implications for aspiration of venous air. We again found that only the Bunegin-Albin multi-orifice catheter allowed retrieval of most of the dose of intravenously infused air and resuscitation from a lethal dose of venous air in most dogs. The Swan-Ganz® catheter and the Arrow® multi-orifice catheters were largely ineffective for either purpose.

In the present study the incidence of successful resuscitation was directly related to the amount of air retrieved and was inversely related to the resistance to flow through the catheters. These correlations are consistent with those reported in our previous study in prone dogs (1) and also with those reported in a recent study in upright dogs using single and multi-orifice introducer sheaths (7). We did not investigate whether the amount of air retrieved with the Bunegin-Albin catheter was greater because there were more side orifices than with the Arrow® or Swan-Ganz® catheter or because it had the lowest resistance of the catheters studied (see Table). We conclude, however, that the Bunegin-Albin multi-orifice catheter may permit a greater portion of VAE to be retrieved and improve the success rate for resuscitation from a fatal VAE dose compared to the Arrow® or Swan-Ganz® catheters in patients undergoing a craniotomy in the sitting position.

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ANESTH ANALG
1989;68:302–7

Evaluation of Pentamorphone in Humans: A New Potent Opiate

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GLASS PSA, CAMPORESI EM, SHAFRON D, QUILLT, REVES JG. Evaluation of pentamorphone in humans: a new potent opiate. Anesth Analg 1989;68:302–7.

We evaluated the analgesic properties of 14-beta-n-pentylaminomorphinone (pentamorphone), a new morphinan derivative, in 23 male volunteers divided into 6 groups who were given either placebo (1 per group) or 0.015, 0.03, 0.06, 0.12, 0.24, 0.48 ug·kg^{-1} pentamorphone intravenously. Analgesia was evaluated by the maximal tolerance to a spring-loaded rod on the tibia and manubrium. Analgesic assessments and arterial blood samples were taken prior to and at set time intervals following drug administration. Pentamorphone produced a linear increase in pain tolerance with increasing dose as well as a dose-dependent depression of ventilation. Pentamorphone had no effect on blood pressure or heart rate in the doses used. Plasma histamine levels at 5 minutes were not elevated with any of the dosages. Pentamorphone appears to be an analgesic with clinically tolerable side effects in the range 0.12 to 0.24 μg·kg^{-1} that merits further evaluation under clinical conditions.

Key Words: ANALGESICS, pentamorphone. PAIN, experimental.

The treatment of acute postoperative pain remains far from ideal (1). This is due to a variety of factors, but central to all pain management programs there is either a lack of efficacy with enhanced safety, or substantial efficacy with a narrow therapeutic index. This has resulted in a search for analgesic compounds with enhanced efficacy and improved safety. Previous tests utilized to evaluate analgesic activity in human volunteers have been controversial (2). Newer methods (3,4) are often extensive, not readily repeatable, and require complex equipment. Using pentamorphone (14-beta-n-pentylaminomorphinone—previously RX77989), we present analgesic properties. Pentamorphone is a morphinan derivative that has been evaluated in animals for its analgesic efficacy. In animal studies, pentamorphone had: 1) an analgesic activity two to eight times greater than that of fentanyl, 2) a therapeutic index ten times greater than fentanyl, and 3) less respiratory depression than fentanyl at equivalent analgesic doses (Unpublished data: Anaquest Investigators brochure). Because of the advantages seen in animal studies, pentamorphone was evaluated for its analgesic efficacy and safety in human volunteers.

Methods

Institutional Review Board approval was obtained for the protocol and each volunteer signed a written informed consent. The study design was double blind and included ascending doses, with four subjects at each dose level. Within each dosage level, three subjects received active drug and one subject placebo. The study consisted of 23 male volunteers divided into six groups given either placebo or 0.015, 0.03, 0.06, 0.12, 0.24, 0.48 μg·kg^{-1} of pentamorphone. (There was no placebo in the 0.015 μg·/kg dose group.) The lowest dosage level was completed prior to entering subjects to the next dosage level. All subjects were screened to assure normal health and normal hepatic, renal and hematological function as assessed by blood chemistries. All biochemical, hematological and urine tests were repeated 1, 3 and 7 days following drug injection. A 12-lead EKG was recorded during the initial screening and repeated the day following drug administration. Subjects were excluded if they were younger than 18 or older than 40, were female, or had a history of anesthesia, opiate

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or recreational drug use within the previous eight weeks. All subjects were also instructed to avoid the use of any over the counter medication, alcohol, tobacco, or any caffeine containing substances for at least 24 hours prior to the study. The night prior to the study the patients were admitted to Duke University Clinical Research Unit where they fasted. On the morning of the study monitoring was instituted. This consisted of a radial arterial line, a nasal cannula, EKG and a finger pulse oximeter. Blood pressure, end tidal CO_2, finger SaO_2 and heart rate were continuously recorded on a Grass model 7 strip chart. Arterial blood samples for blood gas analysis and histamine levels were taken prior to drug administration and 5, 10, 20, 60, and 360 minutes following drug administration. Analgesia was assessed by determining the maximal tolerance to periosteal pressure over the anterior surface of the tibia and manubrium using a calibrated spring loaded rod. (5) At each of the two sites the rod was applied twice with a 15-second interval between each application. These readings were obtained prior to drug administration and then repeated 6, 11, 21, 61, 121, 181, 241, 301 and 361 minutes following drug injection. All analgesic assessments in all subjects were done by the same investigator.

Once all instrumentation for monitoring was completed the volunteers rested for 3 to 5 minutes prior to baseline measurements. Once baseline readings were obtained, a 23g needle was inserted into a vein on the dorsum of the dominant hand. The calculated dose of drug was then injected. The amount of drug within the dead space of the needle was immediately flushed with normal saline. The needle was then withdrawn. The site of drug injection was inspected 1, 3 and 7 days following drug administration.

Following drug injection each volunteer was encouraged to freely express any changes they felt. Each volunteer was asked directly if, during drug injection, they felt burning. After 1 and 6 hours a questionnaire dealing with subjective sensations was completed. Subjects returned for followup inspection of their injection site and for repeat blood and urine samples 1, 3, and 7 days following drug injection.

Blood samples for plasma histamine assay were collected and immediately frozen for subsequent analysis using methods previously described (6). Samples for blood gas analysis were immediately placed on ice and analyzed on an IL 1303 blood analyzer.

For the evaluation of the analgesic data, a mean of two readings obtained at each site at each time interval was calculated. This was then compared to the baseline value and the percentage change determined. To evaluate the consistency between the two readings taken each time analgesic tolerance was assessed the percent differences between the two readings was computed (ie the difference between the two readings divided by their mean). The absolute percent difference for all readings at the two application sites were then combined to yield a mean percent difference between the two readings.

Regression analysis of the percentage change in analgesic tolerance for each dose was done at each time interval. The statistical significance of this regression analysis was calculated. Previous studies have indicated that an increase in pain tolerance of 20% is equal to a usual therapeutic analgesic dose (7), whereas a 70% increase in tolerance is seen following an epidural dose of an opiate (7,8). Thus an ED_{50} for a 20% and 70% increase in pain tolerance was calculated. The ED_{50} was calculated for both the manubrium and anterior tibia using logistic regression analysis. For a 20% change, a subject was considered a responder if the pain increase was greater than 20% and otherwise as a nonresponder. A similar coding was done for a 70% change. The ratio of the intercept to the slope is the estimate of ED_{50}. For each dosage group the percent change in analgesic tolerance for the three volunteers were also combined and a mean value calculated at each time interval.

Respiratory frequency was recorded from the strip chart recording end tidal CO_2. At each time interval evaluated, the number of breaths for 30 seconds before the minute mark and 30 seconds after the minute mark were added to calculate rate. Arterial $PaCO_2$ was compared with baseline levels and the percent change calculated. Duration of analgesia was taken as the time from drug injection until the analgesic tolerance returned to $\leq$10% of baseline. The duration of respiratory depression was defined as the time from drug injection until $PaCO_2$ returned to $<$10% of baseline.

For the presentation of our results all subjects who received placebo were treated as a single group. For statistical analysis, $p < 0.05$ was considered significant.

Results

Pentamorphone produced a linear increase in analgesic tolerance with increasing dose at the 6, 11, 21 and 61 min intervals. This dose-response effect was statistically significant at the 6, 11, 21 and 61 minute time intervals. The 6 min dose-response curve is presented in Figure 1. The average maximal increases in pain

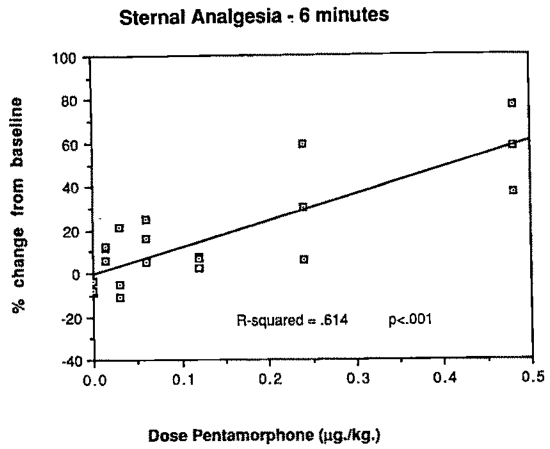

Figure 1. The increase in pain tolerance (as a percent change from baseline) to a spring loaded rod 6 min following the intravenous administration of increasing doses of pentamorphone.

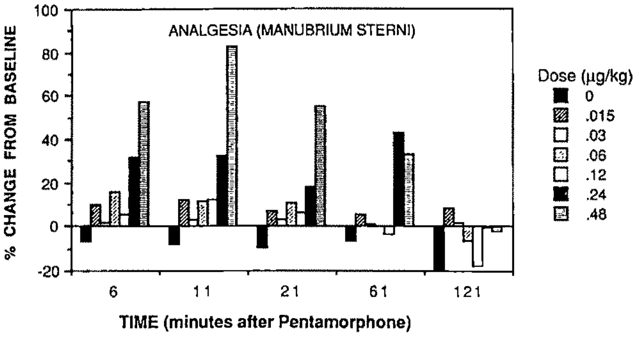

Figure 2. Percent changes (mean) in tolerance to a spring loaded rod applied to the manubrium 6, 11, 21, 61 and 121 min following the intravenous administration of increasing doses of pentamorphone.

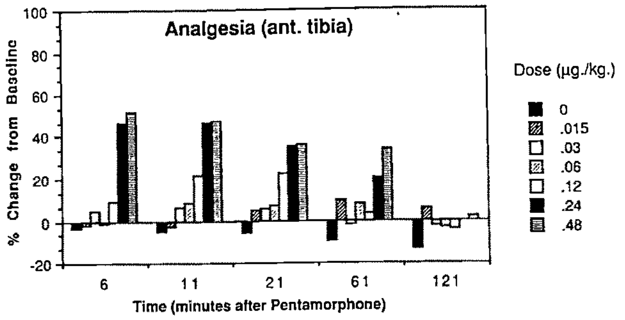

Figure 3. Percent changes (mean) in tolerance to a spring loaded rod applied to the anterior tibia 6, 11, 21, 61 and 121 min following the intravenous administration of increasing doses of pentamorphone.

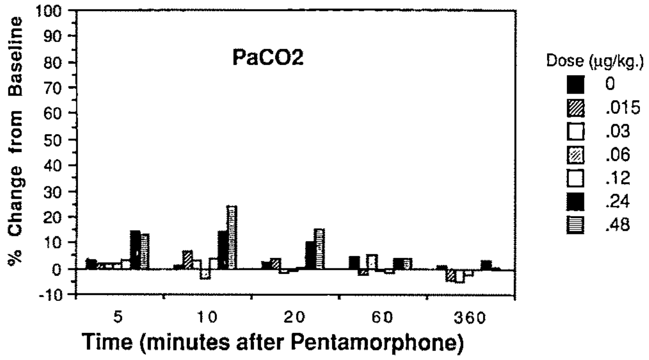

Figure 4. Percent changes (mean) in respiratory rate 5, 10, 15, 20, 60, and 360 min following the intravenous administration of increasing doses of pentamorphone.

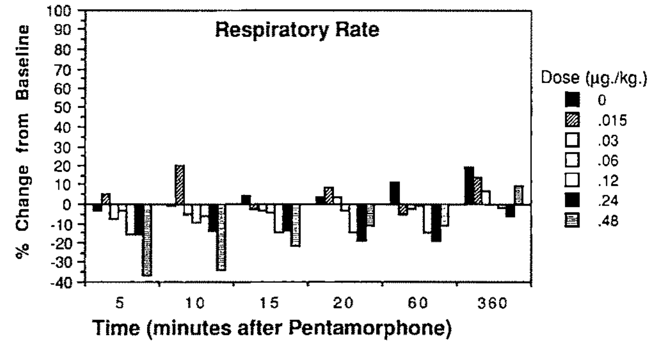

Figure 5. Percent changes (mean) in $PaCO_2$ 5, 10, 20, 60, and 360 min following the intravenous administration of increasing doses of pentamorphone.

tolerance with the 0.12, 0.24, and 0.48 $\mu g \cdot kg^{-1}$ doses were 21%, 47%, 52% on the anterior tibia and 12%, 32%, and 84% on the manubrium, respectively. Composites of the dose-response effect, at each time interval, for the increased tolerance to periosteal pressure on both the anterior tibia and the manubrium are shown in Figures 2 and 3. The peak increase in tolerance to periosteal pressure occurred at the 6 or 11 minute assessment. The increase in tolerance to periosteal pressure was dissipated by the 61 minute assessment with the 0.12 $\mu g \cdot kg^{-1}$ or lower dosages. The 0.24 and 0.48 $\mu g \cdot kg^{-1}$ groups still showed an increase in pain tolerance even at the 61-minute mark but this had dissipated completely by 2 hours. The placebo group showed a slight decrease in analgesic tolerance over the period of the study. The ED_{50} for a 20% increase in pain tolerance was 0.062 µg/kg (tibia) and 0.170 µg/kg (sternum) and the ED_{50} for a 70% increase in pain tolerance was 0.513 µg/kg (tibia) and 0.389 µg/kg (sternum). The slope and intercept were significant at the .05 level except for the slope for 70% ED_{50} for the tibia. The mean absolute percent difference between the two readings obtained with the spring loaded rod on the tibia was 9% and on the manubrium 9%.

Pentamorphone showed a significant dose dependent decrease in respiratory rate and an increase in $PaCO_2$ (Figures 4 and 5). One subject in the 0.24 $\mu g \cdot kg^{-1}$ group and two subjects in the 0.48 $\mu g \cdot kg^{-1}$ group had periods of apnea lasting more than 30 seconds that were associated with decreases in oxy-

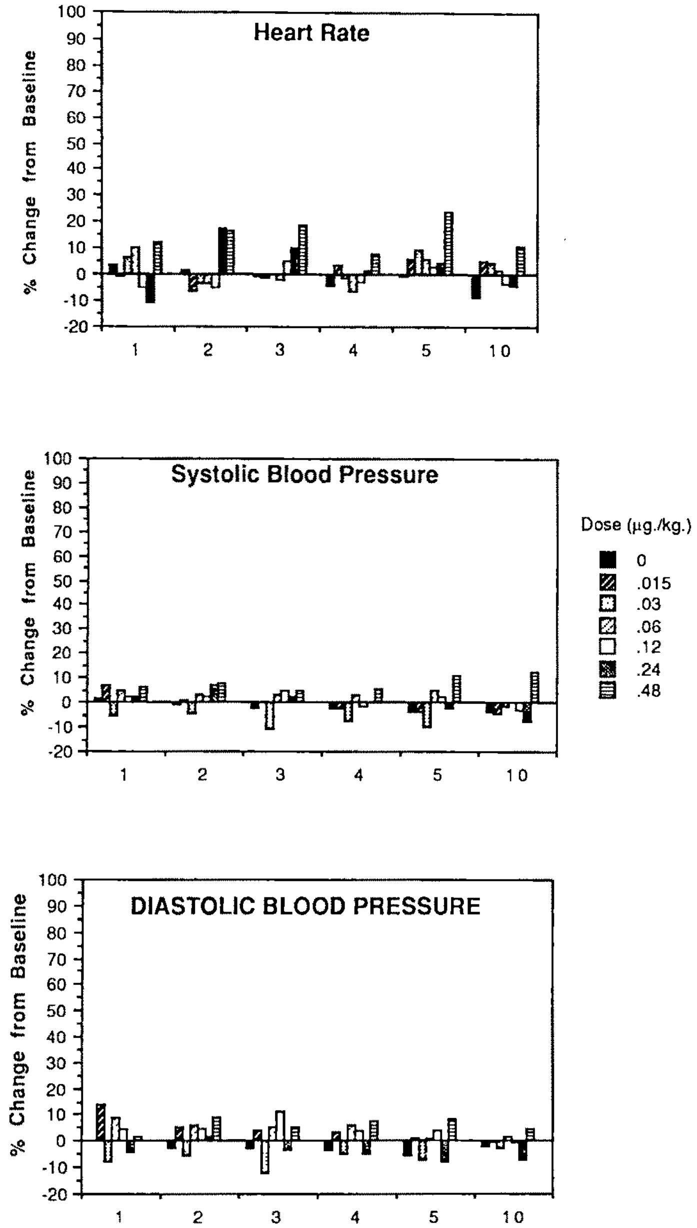

Figure 6. Percent change (mean) from baseline of heart rate, systolic and diastolic pressures at 1, 2, 3, 4, 5, and 10 minutes following the intravenous administration of increasing doses of pentamorphone.

gen desaturation below 85%. These changes all occurred within 10 min of drug administration and all three subjects required verbal prompting to breathe enough to maintain oxygen saturation above 85%. Respiratory depression (increase in $PaCO_2 \geq 10\%$) did not occur up to doses of 0.12 µg/kg of pentamorphone. Following 0.24 µg/kg and 0.48 µg/kg of pentamorphone respiratory depression lasted 20 minutes. Systolic and diastolic blood pressure and heart rate were unaffected by drug administration (Figure 6).

Table 1. Symptoms Following the Intravenous Injection of Increasing Doses of Pentamorphone

	Dose µg/kg						
Symptom	Placebo	0.015	0.03	0.06	0.12	0.24	0.48
Pain on injection	1/5	0/3	0/3	0/3	0/3	0/3	1/3
Headache	1/5	1/3	1/3	1/3	0/3	3/3	1/3
Tiredness	1/5	0/3	0/3	0/3	3/3	3/3	3/3
Euphoria	0/5	0/3	0/3	1/3	1/3	3/3	1/3
Dizziness/Light Headed	0/5	0/3	0/3	1/3	2/3	3/3	2/3
Visual Disturbance	0/5	0/3	0/3	0/3	1/3	3/3	2/3
Nausea	0/5	0/3	0/3	0/3	0/3	2/3	0/3

Subjective symptoms expressed by the volunteers are summarized in Table 1. Visual disturbances were generally described as "a loss of horizontal hold". Subjects with visual disturbances all had vertical nystagmus that resolved within minutes. Pentamorphone did not produce pain on injection. Of the two subjects that had nausea one also vomited. In both, nausea lasted less than 10 minutes. Tiredness and dizziness were common subjective feelings, especially at doses of 0.12 $\mu g{\cdot}kg^{-1}$ or greater. The spring loaded rod resulted in all subjects having some minor bruising and tenderness over the areas tested which resolved over a few days.

Plasma histamine levels were similar before and five minutes following drug administration at all dosage levels. There was also no clinical evidence of histamine release. Follow-up inspection of the injection site showed no evidence of thrombophlebitis at 1, 3 or 7 days. There were no changes in biochemical or hematological tests that could be ascribed to drug administration. There were also no changes seen in the followup 12 lead EKG.

Discussion

The development of new analgesics over the past 20 years has taken several directions. With morphine as the standard. development has been toward: 1) more potent agents, 2) more hemodynamically stable agents, 3) shorter or longer acting agents, 4) agents with partial agonist/antagonist actions, and 5) agents with affinity for specific opiate receptor subtypes. The obvious primary goal of the development of any new analgesic is increasing effectiveness against pain in a dose-dependent manner without hemodynamic or respiratory depression. Besides avoidance of respiratory and cardiovascular depression other features may be desirable in analgesics. These include minimal nausea and vomiting, absence of rigidity when used at high doses, and either combined analgesic and hypnotic actions for use during anesthesia or an absence of any sedative effect when used purely as an analgesic. Ideally any new analgesic should provide an advantage over previously available opiates. Studies of pentamorphone in animals tend to imply a greater ED_{50}/LD_{50}.

This initial human study was designed primarily to evaluate efficacy and safety of pentamorphone. Beecher (2), in his review of experimentally induced pain, was pessimistic as to the ability of algesimetry to show a dose-response effect for potent analgesics. More recent work (3–5,7,10), however, has shown that algesimetry can be utilized in determination of analgesic efficacy. The spring-loaded rod has been used by several investigators to evaluate experimentally induced pain (5,7,8,10). Our study confirms that this method provides an easily discernible dose-response effect. The spring loaded rod, because it can be readily repeated, also enabled us to determine the duration of analgesic effect. Thus, we were able to define both magnitude and duration of analgesic efficacy. Our results were in close agreement with the original animal work.

Individuals differ both in their pain thresholds, as well as in their responses to analgesics. This, combined with the fact that an experimentally induced form of pain was utilized to assess the potency of pentamorphone, makes it difficult to predict a likely therapeutic dose for pentamorphone. There are, however, studies that have employed the same method with known analgesics (7,8). From these studies it appears that a therapeutic dose of a known analgesic (5.0 mg of intravenous methadone or 0.5 mg intravenous hydromorphone) will provide a maximal 20% increase in pain tolerance to a spring-loaded rod (7). Epidural narcotics (e.g., morphine and sufentanil) produce a 70% increase in pain tolerance to a spring-loaded rod (7,8). Therefore, we calculated the ED_{50} for both a 20% and 70% increase in pain tolerance to provide some indication of the likely clinical analgesic dose range for pentamorphone. Consequently, assuming a 20% increase in pain tolerance is a measure of the dose needed for clinical analgesia, the dosage range of pentamorphone can be predicted to be 0.05–0.2 μg/kg. This also implies that pentamorphone is 500–700 times more potent than morphine.

Although we did not employ sensitive measures of respiratory control, our methods were sensitive enough to demonstrate that, like other potent opiates, pentamorphone produces a dose dependent respiratory depression. This respiratory depression appears to be shorter-lasting than its analgesic action. More sensitive tests of respiratory function are necessary to fully describe the effects of pentamorphone on ventilatory control. Pentamorphone caused minimal alteration in cardiovascular parameters. In this study only simple measures were used; full hemodynamic monitoring over a wide dose range will be necessary to describe in complete detail its cardiovascular effects.

The vertical nystagmus observed in some of our subjects is not commonly seen with other opiates. This sign, however, was extremely common following the administration of higher doses (0.12 or greater) of pentamorphone. The onset of the vertical nystagmus seemed to correspond with the onset of other general symptoms of central opioid action. Nystagmus, however, lasted only briefly. It is uncertain whether this effect was related to an opiate action or whether it was unique to pentamorphone. All other symptoms expressed by the volunteers were those expected of a potent opiate agonist. The adverse effects (bruising and tenderness) produced by repeated measures with the spring loaded rod were acceptable to the volunteers and never produced permanent tissue damage.

We propose that the combinations of tests utilized in this study provide simple and useful means to evaluate and compare analgesics. We also demonstrated that pentamorphone is a new synthetic opiate with extremely potent analgesic activity. Its likely therapeutic range for postoperative pain is .05 to 0.2 $\mu g \cdot kg^{-1}$. At this dose it shows clinically acceptable respiratory or cardiovascular alterations. Further studies to fully characterize its relative analgesic potency, and respiratory and hemodynamic effects in humans are warranted.

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Accuracy of Laser Doppler Capillary Flow Measurements for Predicting Blood Loss from Skin Incisions in Pigs

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CARPENTER RL, KOPACZ DJ, MACKEY DC. Accuracy of laser Doppler capillary flow measurements for predicting blood loss from skin incisions in pigs. Anesth Analg 1989;68:308–11.

This study assesses the clinical applicability of laser Doppler capillary flow measurements for predicting blood loss from a surgical incision. To produce a wide range of blood flows, we injected lidocaine 1%, lidocaine 1% plus octapressin (0.03 $IU{\cdot}ml^{-1}$), and lidocaine 1% plus epinephrine (5 $\mu g{\cdot}ml^{-1}$) subcutaneously into three separate sites on the flank of each animal (N = 6). Laser Doppler flow measurements were made before and 10 minutes after injection Subcutaneous injection of lidocaine tended to increase cutaneous blood flow (96 ± 13 to 153 ± 30 mV, mean ± SE, P = 0.09). Blood flow tended to decrease after injection of lidocaine with epinephrine (101 ± 13 to 57 ± 10 mV, P = 0.03) or octapressin (108 ± 20 to 58 ± 11 mV, P = 0.08). Laser Doppler measurements were higher after the injection of plain lidocaine than after that of lidocaine with either epinephrine or octapressin (P = 0.004). A standard incision was performed at each site and blood loss measured over the subsequent 10 minutes. Laser Doppler measurements correlated with the amount of bleeding from the surgical incision (R = 0.69, $P < 0.001$). We conclude that the laser Doppler is a useful tool for evaluating the ability of subcutaneously injected local anesthetics (vasodilators) or vasoconstrictors to alter bleeding from skin incisions.

Key Words: ANESTHETICS, LOCAL—lidocaine. SYMPATHETIC NERVOUS SYSTEM—pharmacology, epinephrine, vasoconstrictors.

Capillary blood flow has a major effect on absorption of and duration of action of local anesthetics and on the amount of surgical bleeding. Although many methods, including plethysmography and xenon washout, have been employed to quantitate changes in capillary blood flow, all have shortcomings (1–4). The laser Doppler capillary perfusion monitor is a relatively new method that is reported to measure capillary blood flow accurately, and noninvasively.

Laser Doppler capillary perfusion monitors function by directing a laser light beam on the skin and evaluating the reflected light. Laser light reflected from moving cells undergoes a frequency shift as a result of the Doppler effect (5,6). The magnitude of this "Doppler shift" is directly proportional to the velocity and mass of erythrocytes in the capillary bed and linearly correlates with blood flow (2,3,7–10). However, because the laser Doppler measures velocity of red cell movement rather than total blood flow, its accuracy for clinical applications has been questioned.

In this study, we assess the clinical applicability of laser Doppler capillary flow measurements by 1) creating a wide range of skin blood flows by injecting vasodilating or vasoconstricting solutions into the dermis; 2) using the laser Doppler to measure the skin blood flow in the injected areas; and 3) correlating laser Doppler measurements with blood loss from a standard surgical incision made in the injected area.

Methods

After approval of our Animal Care and Use Committee, six pigs weighing 12.8–14.0 kg were anesthetized with intraperitoneal thiamylal (25–40 $mg{\cdot}kg^{-1}$). Anesthesia was maintained with an intravenous infusion of methohexital and core temperature was maintained through the use of a heating pad and by controlling ambient temperature. Three test solutions were used to alter skin blood flow: lidocaine 1% for vasodilation, and lidocaine 1% with epinephrine 5 $\mu g{\cdot}ml^{-1}$ and lidocaine 1% with octapressin 0.03

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IE·ml^{-1} for vasoconstriction. We chose both epinephrine and octapressin because these vasoconstrictors have different sites of action in the microcirculation. The dosages were chosen because our preliminary studies indicated that they effectively reduce laser Doppler capillary flow measurements.

Each lidocaine solution (10 ml total volume) was subcutaneously injected into one of three 3 × 7 cm test sites on the flank of the animal. The three test sites were separated by a minimum of 7 cm, were randomly assigned, and investigators were blinded to the identity of the solution injected. Immediately before and 10 minutes after injection, capillary blood flow was measured in triplicate at each site (at both ends and in the middle) with a laser Doppler capillary perfusion monitor (Medpacific LD5000). This monitor measures blood flow to a depth of 1 mm over a surface area of approximately 1 mm^2 (total area 1 mm^3). The three blood flows measured at each site were averaged. A 5 cm incision completely through the dermis was then made in the center of each site. One investigator performed all incisions. Incision sites were blotted once a minute for 10 minutes. Blood loss was estimated by the weight of blood absorbed by the gauze pads. Correlation coefficients were determined for the laser Doppler flow measurements determined 10 minutes after injection (i.e., immediately prior to incision) and blood loss at each site. The effectiveness of lidocaine as a vasodilator and of lidocaine plus either epinephrine or octapressin as vasoconstrictors was assessed by paired *t* test. Differences in blood flow prior to and 10 minutes after injection and in blood loss were assessed by analysis of variance.

Results

Baseline blood flows (i.e., prior to injection) were similar in the sites injected with the three different test solutions ($P = 0.87$, Table 1). Injection of lidocaine 1% produced a 62 ± 35% (mean ± SE, $P = 0.09$) increase in capillary blood flow. Capillary blood flow decreased from baseline by 36 ± 9 ($P = 0.03$) or 34 ± 20% ($P = 0.08$), when either epinephrine or octapressin was added to the injected lidocaine, respectively. The mean coefficient of variation for the measurements at the three sites that were averaged was 0.16 for lidocaine, 0.19 for lidocaine with epinephrine, and 0.15 for lidocaine with octapressin. The range of laser Doppler measurements at the time of surgical incision was effectively widened, those sites injected with lidocaine having higher readings than those injected with lidocaine with either epinephrine or octapressin (Table 1, $P = 0.004$).

Table 1. Effect of Subcutaneous Injection of Lidocaine 1% Plain (L), With Epinephrine 5 μg·ml^{-1} (L + E) and With Octapressin 0.03 IE·ml^{-1} (L + O) on Cutaneous Blood Flow and Blood Loss After Surgical Incision

	Laser Doppler Blood Flow		
Drug	Baseline (mV)	After Injection (mV)	Blood Loss (ml)
L	96 ± 13*	153 ± 30*	3.0 ± 0.7‡
L + E	101 ± 13§	57 ± 10†	1.7 ± 0.5‡
L + O	108 ± 20‖	58 ± 11†	1.5 ± 0.5‡

*$P = 0.09$; †$P = 0.004$; ‡$P = 0.15$; §$P = 0.03$; ‖$P = 0.08$. Values are mean ± SE.

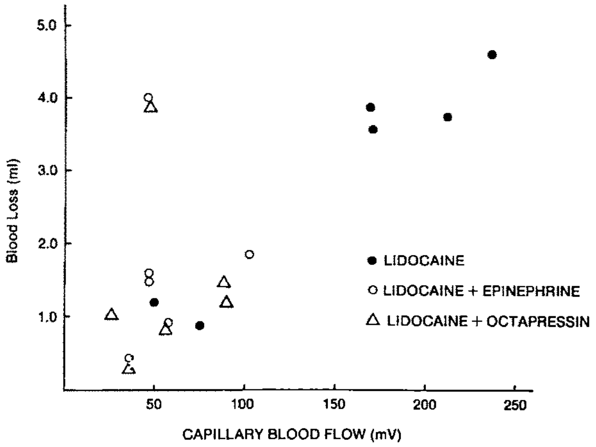

Figure 1. Correlation of laser Doppler blood flow measurements with blood loss from a standard surgical incision.

Laser Doppler blood flow measurements were directly proportional to blood loss at 16 to 18 incision sites (Fig. 1, $R = 0.69$, $P < 0.001$). Two of the 12 sites injected with vasoconstrictor (1 octapressin and 1 epinephrine) had large blood losses, despite low blood flows, probably reflecting the presence of an unusually large artery or vein that resulted in excessive bleeding. Although blood loss at the sites injected with lidocaine with epinephrine or octapressin was decreased by 38 ± 22% and 47 ± 14%, respectively, this difference was not statistically significant (Table 1, $P = 0.15$).

Discussion

Many reports have documented the accuracy of laser Doppler flow measurements. Studies using hydraulic models with known red cell velocities indicate that laser Doppler flow measurements are linearly related to flow (8). Similarly, clinical studies have demonstrated correlation coefficients of 0.8 to 0.98 between laser Doppler measurements and measurements derived from electromagnetic flow probes (1), photoplethysmography (7), xenon washout (2,9), and plethysmography (3).

Nevertheless, because the laser Doppler measures blood velocity, not flow, some investigators have questioned its accuracy in the clinical setting. Regardless of the component of flow that the laser Doppler actually measures, we found a good correlation between the laser Doppler measurements of skin capillary blood flow and an important clinical outcome—blood loss. This correlation is impressive, considering the crude methodology associated with blood loss techniques and the wide variability usually found in clinical studies that assess blood loss (11).

Octapressin and epinephrine are both effective vasoconstrictors that have previously been shown to reduce surgical blood loss (11,12). Epinephrine is a more potent constrictor of precapillary sphincters, whereas octapressin acts primarily on capacitance vessels (12,13). Despite the different mechanisms of action, the reduction in capillary blood flow was similar with the two drugs. The fact that the reduction in flow correlated directly with the reduction in blood loss, regardless of the site of action of the vasoconstrictor, further supports our conclusion that the laser Doppler is an accurate method for assessing the effects of subcutaneous injection of vasoconstrictors and vasodilators on cutaneous blood flow.

Although we found a trend for blood loss to be decreased when epinephrine or octapressin was added to lidocaine, this trend was not statistically significant. The lack of statistical significance resulted in part from the wide variability in blood loss from our incisions. However, the variability in bleeding is largely explained by the variable effect on cutaneous blood flow. For example, sites injected with lidocaine had a fourfold variation in blood loss. Yet, this variation in blood loss correlated almost linearly with the fourfold variation in blood flow that resulted from the lidocaine injection (Fig. 1). Thus, variability in the effect of lidocaine on cutaneous blood flow appears to account, in part, for the variability in blood loss we observed. Finally, when a maximal decrease in blood loss is desired, injection of solutions of epinephrine or octapressin without added lidocaine might be expected to produce a greater reduction in cutaneous blood flow and may further decrease blood loss (11).

Laser Doppler flow measurements have limitations. The monitor is sensitive to motion artifact. Measurements may lose their linear relationship to flow when there are high volume fractions of red cells in tissue (e.g., lips and fingertips) (8). Variations in oxygen tension have a small effect on flow readings: a 5% coefficient of variation for the PO_2 range of 40–120 mm Hg (8).

One of the most important limitations lies in the fact that skin blood flow varies considerably between sites (14,15). This variability most likely is explained by differences in both capillary density and perfusion. One mm^3 of skin can contain from 16 to 64 capillary loops, of which 15 to 75% are perfused at any one time (16). Although we did not measure blood flow over each 1 mm increment of tissue, our method of averaging three readings provided a practical alternative for estimating the blood flow at each site.

In conclusion, we found that laser Doppler measurements of capillary blood flow correlate with an important clinical outcome: blood loss after skin incision. These results suggest that the debate regarding velocity and flow is irrelevant. We believe that the laser Doppler is a useful tool for assessing the effect of subcutaneous injection of vasoactive drugs on skin blood flow and surgical bleeding. In addition, if our results in pigs can be extrapolated to humans, both octapressin and epinephrine appear capable of reducing skin blood flow when added to lidocaine 1%.

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Effect of Epidural Lidocaine on Spinal Cord Blood Flow

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The effect of epidural lidocaine on spinal cord blood flow (SCBF) was measured in mongrel dogs. Spinal evoked potentials were used to measure spinal cord conduction and enabled us to time the measurement of SCBF associated with maximum reduction in latency and amplitude of spinal evoked potentials produced by instillation of 5 ml of 2% lidocaine in the epidural space. We used the radioactive microsphere technique to quantitate SCBF in the cervical, upper thoracic, lower thoracic, and lumbar regions of the spinal cord. A narcotic/relaxant technique was used to eliminate SCBF changes associated with other anesthetic agents. Other parameters known to affect SCBF were kept constant and within normal physiologic values. As compared with saline solution controls, there were significant decreases in SCBF in all the four areas of spinal cord in animals given epidural lidocaine, most marked in the lumbar area.

Key Words: SPINAL CORD—blood flow. ANESTHETIC TECHNIQUE—epidural. ANESTHETICS, LOCAL—lidocaine.

Despite the widespread use of epidural anesthesia, there are still no data describing the effect of epidurally injected local anesthetics on spinal cord blood flow.

The effect of epidural lidocaine on spinal cord blood flow is important for two reasons. First, although the mechanisms controlling autoregulation of spinal cord blood flow are similar to those controlling cerebral blood flow, it is not known what effect epidural lidocaine has on spinal cord blood flow. Second, although the incidence of permanent spinal cord injury after epidural anesthesia is low (1), permanent spinal cord injuries can result from critical decreases in spinal cord blood flow and resultant ischemic-hypoxic damage to the spinal cord (2). Hence, it is important to know what effect epidural lidocaine itself has on spinal cord blood flow.

To determine the effect on spinal cord blood flow of lidocaine injected into the epidural space, we measured spinal cord blood flow in mongrel dogs before and after injection of 5 ml of either 2% lidocaine or normal saline solution through a catheter placed in the lumbar epidural space.

Preparation Methods

After Institutional Review Board approval, general anesthesia was induced in eight adult mongrel dogs (10–20 kg) with sodium pentobarbital 10 mg/kg intravenous. After tracheal intubation, maintenance of analgesia and stable hemodynamics were obtained with use of an intravenous loading dose of 100 μg/kg of fentanyl followed by a continuous intravenous infusion of 15–30 μg/kg per hour. Paralysis was maintained with intermittent injections of succinylcholine. Respiration was controlled with the use of a Harvard pump to maintain PaO_2 at 80–100 mm Hg, pH 7.35–7.40, and $PaCO_2$ 35–40 mm Hg using humidified room air. Temperature was monitored rectally and maintained between 36° and 37° C by means of a warming blanket. A catheter was advanced through the left femoral artery into the aorta for blood pressure measurements and arterial blood samples. The electrocardiograph (ECG) was monitored with the use of four skin electrodes. A left thoracotomy was performed with an incision in the fourth left intercostal space, and a catheter was placed in the left atrium and sutured in place. The thorax was closed in layers and the left atrial catheter exteriorized through the wound. Left atrial pressure and aortic pressure were transduced with use of Statham pressure transducers. ECG, arterial blood pressure, and left atrial

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pressure were monitored continuously with use of a Gould four channel polygraph.

A 4 mm laminotomy hole was drilled in the lamina of T_{12} and an 18 g Teflon catheter advanced into the epidural space with the tip at the level of the L3 vertebra with use of the technique described by Lebeaux (3). Two epidural electrodes (Avery Laboratories, Farmingdale, NY) were advanced through the same laminotomy hole to lie 5 cm caudad and 5 cm cephalad to the catheter tip. Two needle electrodes (Grass) were used for cephalic recording with one electrode at the intersection of midline and interauricular planes and a second electrode at the tip of the nose. A reference electrode was placed in the skin near the entrance of the laminotomy hole. The sciatic nerves were dissected out bilaterally, and two needle (Grass) electrodes separated by 1 cm were inserted (cathode proximal) into both nerves and sutured in position.

Protocol

After surgical preparation, baseline blood gas tensions were measured with continuous monitoring of aortic blood pressure, ECG, left atrial pressure, and temperature. Microspheres were injected for measurement of baseline spinal cord blood flow (see Methods of Measurements). Recordings of baseline spinal evoked potentials were then made with use of a Nicolet Pathfinder II as described in Methods of Measurements. The dogs were then randomly assigned to receive either 5 ml of 2% preservative free lidocaine or 5 ml of preservative free normal saline solution through the epidural catheter. Evoked potentials were measured at 5-minute intervals until maximum loss of amplitude and latency had occurred in the lidocaine treated group, at which time microspheres were again injected. Lactated Ringer's solution at 37°C was infused intravenously, as necessary, to maintain left atrial pressure at baseline levels. Repeat injection of microspheres was performed at 30 minutes in the saline-treated dogs. This was the mean time required to maximum loss of amplitude and latency of evoked potentials in the lidocaine treated group.

The animals were killed by injection of 40 mEq potassium chloride through the left atrial catheter after the final injection of microspheres. Epidural catheter and epidural electrode placement were verified by dissection prior to removal of the spinal cord completely. The spinal cord was dissected free of its coverings and divided anatomically into lumbar, upper thoracic (T_1 to T_6), lower thoracic (T_6 to T_{12}) and cervical regions. Tissue samples were taken from both right and left diaphragms and kidneys to verify adequate mixing of the microspheres. The radioactivity in each reference blood and tissue sample was measured in a Hewlett Packard gamma scintillation spectrometer, using window settings selected to correspond with the peak energies of each radioactive nuclide. Blood flow per wet tissue sample was determined using counts per milliliter per minute for the blood samples and counts per minute for the tissue sample. Spinal blood flow (Q_{SCBF}) was calculated using the following formula:

$$Q_{SCBF} = Q_r \cdot C_{sc} / Cr,$$

where spinal cord blood flow is milliliters of blood/100 g wet tissue/minute, Q_r = reference blood flow (milliliters/minute), C_{sc} = counts/minute) in spinal cord tissue, and Cr = counts/minute in the reference blood flow. Spinal cord blood flow (milliliters/minute) was divided by the weight of the spinal cord section and was expressed as milliliters/minute per 100 g of spinal cord tissue.

Methods of Measurement

Carbonized microspheres 15 ± 1 μm (SD) in diameter and labelled with gamma emitting in diameter (Sn^{113}, Ru^{103}, Sc^{46}) (4,5) were injected to measure spinal cord blood flow. The microspheres were obtained as 1 mCi of each nuclide in 10 ml of 10% dextran and 0.01% polysorbate 30 (3M) and were diluted in 10% dextran so that 1.0 ml contained approximately 3.0×10^6 microspheres. Before each injection, the microspheres were mixed by alternate agitation for at least 15 minutes in an ultrasonic bath (3M, model DA 0950) and a Vortex agitator. A volume of 1.0 ml of the microsphere suspension was injected into the left atrium in 10–15 seconds, and the atrial catheter was flushed with 5.0 ml of isotonic saline solution. Beginning simultaneously with each microsphere injection and continuing for 90 seconds, a reference blood sample was collected in counting vials from the aortic catheter, at a constant rate, with the use of a Harvard withdrawal pump. Serial injections of the microspheres resulted in no change of heart rate during the interval of injection and no change in aortic or left atrial pressure measured immediately before and after collection of the reference blood samples.

Evoked potentials were measured with 100 μ seconds retangular pulses at a rate of 5.4/second and current setting of 30 mA applied to the sciatic nerves. The sciatic nerves were stimulated bilaterally with, due to use of succinylcholine, no detectable muscle twitch. The three channel recording montage included two channels of spinal responses (below and above the site of anesthesia) and the single scalp response. Analysis time was 30 ms (inter-sample interval = 60 μsec) with LF and HF at 30 and 3 K Hz respectively. Five hundred responses were averaged; this sum was required to resolve the scalp response (1–2 μV). The spinal responses were stable after 20–40 stimuli due to their high amplitude (20–50 μV) and low noise. All responses were replicated twice at each period of data collection.

Statistical Methods

Baseline spinal cord blood flow before the injection of epidural lidocaine or epidural saline solutions was compared with spinal cord blood flow 30 minutes after injection of either lidocaine or saline solution in each of the four areas of the spinal cord. Student's paired *t* test was used to determine whether there was a statistically significant change in spinal cord blood flow after either epidural saline solution or epidural lidocaine.

Results

Baseline values of pH, PO_2, PCO_2, temperature, left atrial pressure, and mean arterial pressure were within physiologic range in all animals. No significant change from these baseline values occurred in any of the eight animals at 30 minutes after epidural injection of saline solution or 2% lidocaine.

In the saline solution group, there were no significant changes in amplitude or latency of spinal evoked potentials within the 30 minutes after injection of preservative free normal saline solution into the epidural space. In the lidocaine group, there was a significant increase in latency and decrease in amplitude after epidural lidocaine. By 30 minutes, the amplitude of the P_1N_2 complex had decreased to 0 both at the rostral spinal recording site and at the scalp-nose channel (Fig. 1).

There was no significant difference in blood flow to any area of the spinal cord in the group receiving epidural saline solution 30 minutes after injection (Table 1). In contrast, blood flow to the cervical, upper thoracic, lower thoracic, and lumbar spinal cord decreased significantly after lumbar epidural instillation of 5 ml of 2% lidocaine ($P < 0.05$) (Table 1) and was most marked in the lumbar region (Fig. 2).

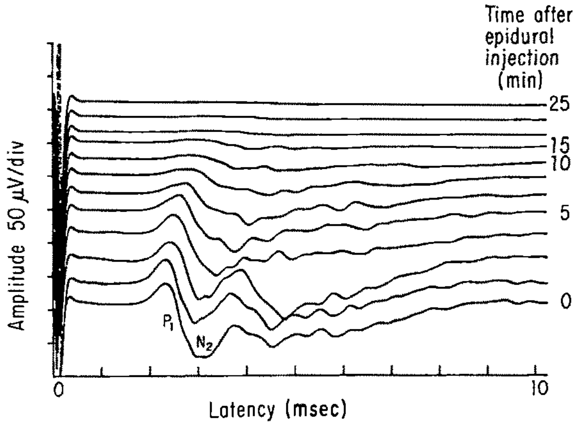

Figure 1. Evoked spinal responses from cephalad electrode before (time 0 min) and after (time 25 min) epidural injection of 5 ml 2% lidocaine, the P_1N_2 amplitude decreases with time until complete obliteration at 25 min.

Discussion

This study showed that small but significant decreases in spinal cord blood flow occur 30 minutes after injection of 5 ml 2% lidocaine epidurally in dogs. Conversely, injection of 5 ml of saline solution into the epidural space of the control dogs was not associated with a significant change in spinal cord blood flow after 30 minutes in any of the four areas of the spinal cord.

Previous investigators have established the major factors involved in regulation of blood flow in the spinal cord. In essence, if the physiologic variables of blood pH, PO_2, PCO_2 and body temperature are kept constant and within the normal physiologic range, and if mean arterial blood pressure is kept between 60–160 mm Hg, then spinal cord blood flow is tightly controlled by local autoregulation within the spinal cord (6–8). These variables did not change significantly in this study, and, hence, the changes in spinal cord blood flow that occurred were probably not related to changes in these variables.

Ours is the only study thus far that has measured changes in spinal cord blood flow after epidural injection of a local anesthetic. However, other workers (9,10) have measured changes in spinal cord blood flow after subarachnoid lidocaine. In one of these studies (9), spinal cord blood flow increased after subarachnoid lidocaine. Unfortunately, variable doses of pentobarbital were used for maintenance of anesthesia. Barbiturates themselves depress cellular metabolism and cause an associated decrease in spinal cord blood flow (11). Similarly, in another study (10) in which there was no significant change in spinal cord blood flow after injection of lidocaine into the subarachnoid space, halothane was used as the

Table 1. Spinal Cord Blood Flow Mean ± 1 SD (ml/100 g per min) in Four Spinal Cord Regions

	Cervical	Upper Thoracic	Lower Thoracic	Lumbar
Epidural Saline Solution (control group; N = 4) Mean SCBF ± 1 SD (ml/100 g per min)				
Baseline SCBF	17 ± 4.24	15 ± 4.97	14.25 ± 4.2	14.75 ± 3.86
SCBF 30 min after injection	15.75 ± 5.67	13.25 ± 5.9	13 ± 6.05	12.5 ± 3.69
Decrease in SCBF 30 min after injection	−1.25 ± 4.03 NS	−1.75 ± 3.8 NS	−1.25 ± 2.2 NS	−2.0 ± 3.56 NS
Epidural Lidocaine (N = 4)				
Baseline SCBF	15.5 ± 4.65	12.75 ± 5.91	14.25 ± 5.25	21.75 ± 7.0
SCBF 30 min after injection	12.25 ± 4.27	10 ± 6.73	10 ± 6.6	12.5 ± 4.2
Decreases in SCBF 30 min after injection	−3.5 ± 1.89*	−2.75 ± 1.7*	−4.25 ± 1.7*	−9.25 ± 5.18*

*$P < 0.05$ for change in SCBF from baseline. SCBF = spinal cord blood flow.

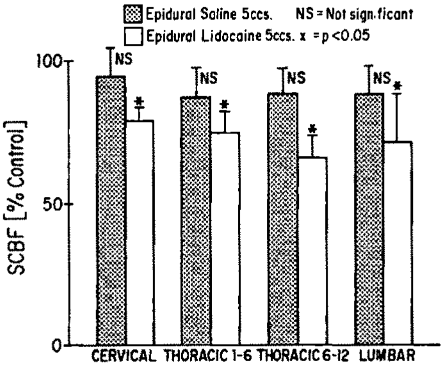

Figure 2. Spinal cord blood flow (SCBF) 30 min after either epidural injection of either saline solution or lidocaine as % of control spinal cord blood flow. Mean ± 1 SE. Lidocaine injection caused a significant reduction of spinal cord blood flow in all four areas of the cord.

anesthetic agent. Halothane increases cerebral blood flow and presumably spinal cord blood flow as well (12). We used a continuous infusion of fentanyl for maintenance of anesthesia, because fentanyl has little effect on spinal cord blood flow as compared with inhalation, barbiturate, or ketamine anesthesia (13).

Baseline values for spinal cord blood flow in this study are similar to those reported in (14). However, although there was a consistent and statistically significant decrease in spinal cord blood flow after the epidural injection of lidocaine, the final value for spinal cord blood flow after epidural lidocaine was still at the lower limit of the normal range of values reported with similar techniques. The decrease in spinal cord blood flow occurred only after epidural lidocaine and did not occur after epidural saline solution.

Baseline values for spinal cord blood flow were higher in our dogs, although within normal limits in the lumbar region of the lidocaine treated animals. It is not clear why blood flow to the lumbar spinal cord was initially higher than that in other areas, but after epidural lidocaine blood flow decreased similarly in all four areas of the cord to approximately equal values.

To discuss the possible causes of the decreases in spinal cord blood flow, it is important to note that lidocaine injected into the epidural space is distributed into three different compartments. The first compartment is the epidural space and lidocaine at a concentration of close to 20 mg/ml bathes the nerves and vessels that cross that space. Lidocaine diffuses from the first compartment into the second compartment consisting of the cerebrospinal fluid and spinal cord tissue. Finally, lidocaine is taken up by vessels crossing the epidural space and enters into the third compartment, the systemic circulation.

The decrease in spinal cord blood flow after epidural lidocaine in our study could be attributed to three factors. First, lidocaine within the spinal cord could have caused the decrease in the metabolic rate for oxygen (MRO_2) of the spinal cord that resulted in a corresponding decrease in spinal cord blood flow. Astrup et al. (15) showed that lidocaine decreases the MRO_2 in dog brain. This decrease was attributed both to its ability to block the sodium/potassium ATP_{ase} pump and to its membrane stabilizing effect. Crosby (16) studied the effects of subarachnoid bupivacaine (an agent closely related to lidocaine) on spinal cord blood flow in conscious rats and found a 27 to 34% decrease in spinal cord blood flow. This was associated with a 3 to 21% decrease in glucose utilization. Additionally, direct blockade of sensory nerves crossing the epidural space and the associated decrease in the frequency of sensory nerve impulses entering the spinal cord may have also decreased spinal cord MRO_2.

A second factor causing a decrease in spinal cord blood flow with epidural lidocaine may be the direct effect of lidocaine on the diameter of blood vessels in the spinal cord and epidural space. Johns et al. (17) used videomicroscopy of in vivo rat cremasteric muscle and showed that whereas 10^0–10^3 μg/ml of lidocaine applied topically caused significant vasoconstriction of arterioles, 10^4 μg/ml caused significant vasodilation. Hence, there is a concentration dependent effect of topical lidocaine on vessel diameter. Interestingly, Bromage (18) found that 100 mg of epidural lidocaine in dogs produced spinal cord tissue concentrations of from 870–125 μg/g, approximately the concentration Johns found to cause vasoconstriction. Conversely, however, in the same study by Johns et al., serum concentrations of intravenous lidocaine of 3.61 ± 0.47 μg/ml produced arteriolar dilation. In a study by Lebeaux (3), dogs given 5 ml of epidural 2% lidocaine had serum levels of 1.8–2 μg/ml. Hence, in this study, in which a similar dose of epidural lidocaine was used, there may be vasoconstriction resulting from the tissue concentrations of lidocaine opposing effects of vasodilation caused by serum concentrations of lidocaine.

We did not measure the serum lidocaine concentrations and could not measure the local effect of lidocaine on vessels in the epidural space or spinal cord, so it is impossible to implicate definitively any of these individual factors; further work could determine whether any or all of these factors are involved.

The third possible factor causing a decrease in spinal cord blood flow after epidural lidocaine may be the effect of an increase in pressure in the epidural space after injection of 5 ml of lidocaine. However, this is unlikely as in this study, a similar volume of saline solution did not produce the same decrease in spinal cord blood flow in the control animals.

What is the significance of the small decrease in spinal cord blood flow that we observed after epidural injection of lidocaine? The safety of epidural anesthesia is well established; in a review of 780,000 lumbar epidural anesthetics, the incidence of permanent neurologic deficits was 0.01% or 1:10,000 (1). These neurologic deficits were attributed to arachnoiditis, epidural hematomas, or so called "watershed" areas of the lumbar spinal cord. In these watershed areas, blood flow is dependent on intercostal arteries supplying the anterior spinal artery. In approximately 15% of the population, the intercostal anastomosis may only be present above the T_9 segmental level. Severe hypotension or occlusion of the anterior spinal artery might, therefore, result in anterior spinal cord ischemia and paralysis. Given the fairly common occurrence of moderate hypotension accompanying epidural anesthesia, it is interesting that neurologic deficits are seen so uncommonly after epidural anesthesia. It is tempting to speculate that the decrease in spinal cord blood flow shown in this study reflects a corresponding decrease in spinal cord metabolic rate and that despite hypotension and watershed areas of blood flow, epidural lidocaine anesthesia confers a degree of protection on the spinal cord. Indeed, intravenous lidocaine has been shown to have a significant beneficial effect when given to cats after compressive spinal cord injury (19).

In summary, our study demonstrates that there is a small but statistically significant decrease in spinal cord blood flow 30 minutes after injection of lidocaine into the epidural space of mongrel dogs. Further work is necessary to delineate the mechanisms of this decrease in blood flow.

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Epidural Hydromorphone With and Without Epinephrine for Post-Operative Analgesia After Cesarean Delivery

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DOUGHERTY TB, BAYSINGER CL, HENENBERGER JC, GOODING DJ. Epidural hydromorphone with and without epinephrine for post-operative analgesia after cesarean delivery. Anesth Analg 1989;68:318–22.

The efficacy of epidural hydromorphone alone or in combination with epinephrine for postoperative analgesia was evaluated in 30 healthy women who underwent cesarean delivery with epidural anesthesia. They were assigned randomly to receive either 1.5 mg hydromorphone alone (N = 15) or 1.5 mg hydromorphone with 1/200,000 epinephrine (N = 15). Duration of analgesia (mean ± SD) was 24.3 ± 9.4 hours after the epidural injection of hydromorphone plus epinephrine. This was significantly greater ($p < 0.01$) than the duration of 18.2 ± 5.9 hours after the same dose of plain hydromorphone. Analgesia was more rapid in onset and significantly better at the 0.5, 1, 3, and 12 hours postoperatively in the hydromorphone-epinephrine group. Side effects including pruritus (73%), nausea (20%), and vomiting (15%) were of similar frequency with and without epinephrine. Although mean venous PCO_2 (P_vCO_2) levels three and six hours after the hydromorphone-epinephrine dose were elevated significantly over the pre-drug P_vCO_2 levels, no respiratory depression was detected by an apnea monitor to which all patients were connected. The addition of epinephrine to epidural hydromorphone hastened onset and prolonged the duration of analgesia after cesarean section.

Key Words: ANALGESICS—hydromorphone
ANESTHESIA—obstetric
ANESTHETIC TECHNIQUES—epidural
PAIN—postoperative

The epidural administration of 1.5 mg of hydromorphone after cesarean delivery provides adequate analgesia lasting 13–19 hours (mean ± SD) (1–3). Although the addition of epinephrine has been reported to improve analgesia in volunteers given epidural morphine (4), it may not improve analgesia when epidural narcotics are given for control of pain after surgery on the lower abdomen (5). In the following prospective, randomized, double-blinded study, we compared the onset, duration, and quality of post-cesarean section analgesia between one group of women given 1.5 mg of epidural hydromorphone and another group given 1.5 mg of epidural hydromorphone plus 1/200,000 epinephrine.

Methods

This study was approved by the Human Use Committee at Winn Army Community Hospital. Written informed consent was obtained from 31 healthy women at term who underwent delivery by cesarean section with epidural anesthesia. With certain exceptions, summarized in the following paragraphs, the methods followed in this study were as described in our earlier report (1).

Operative anesthesia was provided with 3% 2-chloroprocaine administered through a lumbar catheter inserted 2–3 cm into the epidural space. Nalbuphine (10 mg) and droperidol (1.25 mg) were given intravenously to each patient immediately after delivery of her infant to provide sedation and as prophylaxis against nausea. If necessary, the segmental level of the block was increased with 0.25% bupivicaine. The catheter remained in place after surgery. Later, when the patient first requested medication for pain

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relief, she was randomly assigned to receive either 1.5 mg hydromorphone or 1.5 mg hydromorphone plus 1/200,000 epinephrine through the catheter.

Preservative-free hydromorphone hydrochloride (Dilaudid^{R}, Knoll Pharmaceutical Co.) was diluted to 10 ml with sterile normal saline solution (with or without the epinephrine added) and administered through the epidural catheter. The catheter was flushed with 1 ml of normal saline solution. Both the patient and the anesthesiologist were unaware of which preparation the patient was given.

The patient's own assessments of the intensity of her pain were made immediately before the epidural injection and 0.5, 1, 3, 6, 9, and 12 hours thereafter. For each assessment, the patient represented the intensity of her pain by placing a point on a new, unmarked visual analog scale similar to the ones described by Rosen et al. (6) and Scott and Huskinsson (7). This pain intensity score was converted to a value for pain relief and standardized for each patient with use of the following expression (6):

$$\frac{\text{Analog line representing pain before hydromorphone (mm)} - \text{Analog line representing pain after hydromorphone (mm)}}{\text{Analog line representing pain before hydromorphone (mm)}} \times 100$$

$$= \text{\% of maternal pain relief.}$$

The percent of maternal pain relief represented the relative change in pain relief with each patient serving as her own control (6). At each maternal assessment, an observer also evaluated the patient's relief of pain with the use of a five-point rating system described by Rosen et al. (6).

Duration of analgesia was defined as the length of time from the epidural injection of hydromorphone preparation until the patient requested additional pain relief. If the patient desired additional analgesia, she was offered either a second epidural injection of 1.5 mg hydromorphone or an opioid chosen by the attending obstertrician to be given orally or intramuscularly, and the evaluation of the patient was completed. The catheter was removed either immediately after a second epidural injection or 48 hours after its initial placement if a second injection was not performed.

Before the initial dose of hydromorphone solution, an apnea monitor (Sirecust 400, Siemens Medical Systems, Inc., Iselin, NJ) was attached to each patient. The apnea monitor sounded an alarm at a respiratory rate of less than 9 breaths/minute. The apnea monitor was used only while the patient was in bed.

Table 1. Characteristics of the 30 Female Patients Who Received Epidural Hydromorphone or Hydromorphone With Epinephrine for Post-Operative Analgesia After Cesarean Section[a]

	Epidural Administration	
Patient Characteristics	Hydromorphone 1.5 mg (N = 15)	Hydromorphone 1.5 mg Plus Epinephrine 1/200,000 (N = 15)
Age ± SD (yr)	26.1 ± 3.7	25.7 ± 3.9
Height ± SD (cm)	161.2 ± 7.8	159.3 ± 6.8
Weight ± SD (kg)	82.7 ± 18.8	80.1 ± 17.4
First cesarean section	10	9
Repeat cesarean section	5	6

[a] No significant differences between treatment groups.

Immediately before the epidural injection of hydromorphone with or without epinephrine and at 3 and 6 hours afterwards, peripheral venous blood samples were obtained from each patient for measurement of PCO_2 (P_vCO_2). All patients were observed for at least 24 hours after the epidural injection for the appearance of pruritus, nausea, vomiting, urinary retention, and respiratory depression (<9 breaths/minute). Pruritus, if severe enough to be uncomfortable, was treated with intravenous naloxone in increments of 0.1 mg to a total of 0.4 mg. Nausea and vomiting were treated as needed with the same incremental doses of intravenous naloxone. Any patient receiving a second epidural dose of hydromorphone was monitored for respiratory depression for an additional 24 hours.

Demographic characteristics of the patients in the two treatment groups were compared with the use of nonpaired Student's *t* tests and chi-square tests. Wilcoxon rank-sum tests for unpaired data were used to analyze the duration of analgesia, the percentages of maternal pain relief, and observer's assessment of maternal pain relief (8). Comparison of P_vCO_2 levels were made by analysis of variance (7). The incidences of side effects were analyzed by chi-square tests. A P value of less than 0.05 was considered statistically significant.

Results

Of the 31 patients originally entered into our study, one was excluded from the data analysis because her catheter had become dislodged from the epidural space prior to her hydromorphone injection. Fifteen patients remained in each group, and the two groups

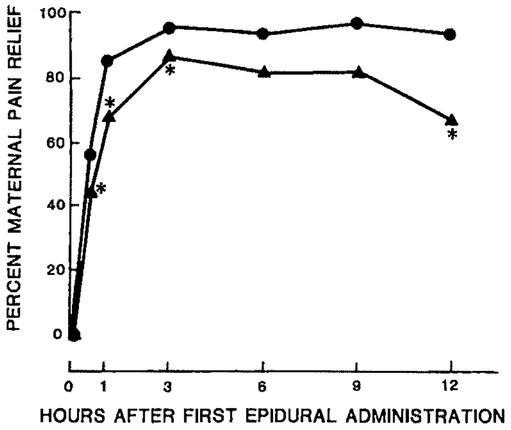

Figure 1. Mean percentages of maternal pain relief after epidural injection of 1.5 mg hydromorphone alone (▲) and 1.5 mg hydromorphone with 1/200,000 epinephrine (●). Standard deviations were omitted because the data at each time interval are not believed to be normally distributed. *Significantly different ($p < 0.05$) by the Wilcoxon rank-sum test.

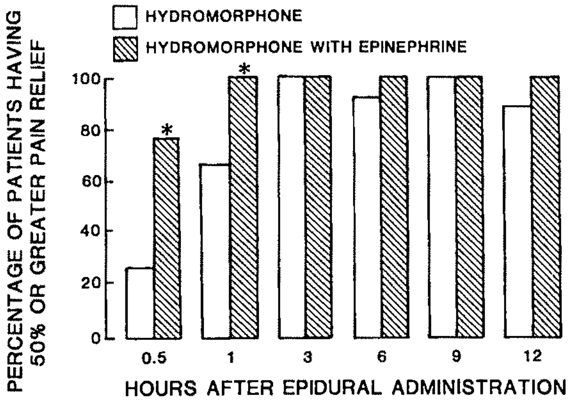

Figure 2. Observer's assessment of maternal pain relief after the epidural injection of 1.5 mg hydromorphone with and without epinephrine. *Significantly different ($p < 0.05$) by the Wilcoxon rank-sum test.

Table 2. Mean Duration of Post-Operative Analgesia and Percentage of Patients Requiring Additional Narcotics After the Epidural Injections of Hydromorphone or Hydromorphone Plus Epinephrine

	Epidural Administration	
Duration	Hydromorphone 1.5 mg (N = 15)	Hydromorphone 1.5 mg Plus Epinephrine 1/200,000 (N = 15)
Mean ± SD (hr)	18.2 ± 4.1	24.3 ± 9.4^a
Range (hr)	12–25	12–40
Percentage of patients requesting additional narcotics	93	53^b

^{a}Significantly different ($p < 0.01$) by the Wilcoxon rank-sum test that included patients not requesting additional narcotics (one in the hydromorphone only group and seven in the hydromorphone plus epinephrine group);

^{b}significantly different ($p < 0.01$) by the Chi-square test.

Table 3. Mean ± SD P_vCO_2 Levels (in millimeters of mercury) Before and After the Epidural Administration of Hydromorphone Alone or Hydromorphone Plus Epinephrine

	Epidural Administration	
Venous PCO_2	Hydromorphone 1.5 mg (N = 15)	Hydromorphone 1.5 mg Plus Epinephrine 1/200,000 (N = 15)
Before injection	33.3 ± 4.2	33.2 ± 2.6
3 h after injection	35.5 ± 3.7^a	37.5 ± 3.6^b
6 h after injection	35.8 ± 4.0^a	39.2 ± 4.1^c

^{a}Not significantly different from venous PCO_2 levels before injection;

^{b}significantly different ($p < 0.05$) from venous PCO_2 levels before injection;

^{c}significantly different ($p < 0.01$) from venous PCO_2 levels before injection.

were similar in age, height, weight, and number of previous cesarean sections (Table 1).

Most patients in both groups reported a marked decrease in postoperative pain during the 12-hour assessment period after their epidural injection of hydromorphone. Maternal pain assessments in two patients in each group were prematurely discontinued 9 hours after the first epidural injection. As illustrated in Figure 1, patients in the hydromorphone-epinephrine group had analgesia more rapid in onset and significantly better at the 0.5, 1, 3, and 12-hour intervals than that reported by the patients in the plain hydromorphone group. Comparison of Figures 1 and 2 shows reasonably good agreement between the patients' own assessments of pain relief and those recorded by an observer. As shown in Table 2, the addition of epinephrine to the hydromorphone solution prolonged the mean duration of analgesia. Moreover, the number of patients requiring additional narcotics for pain relief subsequent to the initial epidural dose was significantly greater in the hydromorphone only group. One patient in the plain hydromorphone group and seven patients in the hydromorphone-epinephrine group needed no additional narcotics during the remainder of their hospital stay.

No respiratory depression was detected in any patient by the apnea monitor throughout the 24-hour observation period. P_vCO_2 levels measured 3 and 6 hours after the administration of plain hydromorphone did not differ significantly from pre-drug levels (Table 3). In contrast, the corresponding P_vCO_2 levels in patients given hydromorphone-epinephrine were elevated significantly over control levels at 3

Table 4. Number of Patients Having Pruritus, Nausea, or Vomiting After the Epidural Administration of Hydromorphone or Hydromorphone With Epinephrine for Post-Operative Analgesia After Cesarean Section[a]

Side Effect After First Epidural Injection	Hydromorphone 1.5 mg No. of Patients (N = 15)	Hydromorphone 1.5 mg Percent	Hydromorphone 1.5 mg Plus Epinephrine 1/200,000 No. of Patients (N = 15)	Hydromorphone 1.5 mg Plus Epinephrine 1/200,000 Percent
Pruritus	11	73	12	80
Nausea	3	20	4	26
Vomiting	2	15	3	20

[a]No significant differences between treatment groups.

hours ($p < 0.05$) and 6 hours ($p < 0.01$) after administration.

Pruritus was the most frequent side effect (Table 4). It was mild in most patients, usually starting on the face and trunk 2.5–3 hours after the epidural injection. However, five patients (three in the hydromorphone-epinephrine group and two in the plain hydromorphone group) requested treatment of the pruritus. One of the patients in the hydromorphone only group requested further pain relief after treatment with naloxone. The presence of epinephrine did not change significantly the incidences of pruritus, nausea, or vomiting. Three patients in the hydromorphone only group and four patients in the other group became nauseated 3–7.5 hours after the injection, and all but two vomited, one in each group. In each case, the nausea and vomiting occurred when the patient either sat or ambulated.

Urinary retention could not be assessed because of the presence of indwelling urinary catheters, which remained in place for up to 24 hours after surgery. Subsequently, two patients in the hydromorphone-epinephrine group were unable to void 23 and 27 hours after the epidural dose and required recatheterization.

Discussion

Bromage et al. (5) found no obvious difference between plain and epinephrine containing hydromorphone in terms of time to onset and duration of analgesia after lower abdominal surgery. This is in contrast to our present study in which the addition of epinephrine to epidural hydromorphone hastened onset and increased the duration of analgesia. The effect of epinephrine on the onset and duration of analgesia may have been difficult for Bromage et al. to assess because diverse surgical procedures may have induced different levels of postoperative pain between their treatment groups. In the present study, the operative procedure (cesarean section) was the same for all patients and was performed by the same group of obstetricians.

Bromage et al. (4) showed in male volunteers that the inclusion of 1/200,000 epinephrine with epidural morphine resulted in cutaneous hypalgesia to ice and pin scratch that was more rapid in onset, more intense, and longer lasting than that seen with plain morphine. Adverse effects also were more frequent and intense in the presence of epinephrine. They suggested that epinephrine reduced the vascular uptake of the morphine, thereby allowing an intensification of spinal cord and brain stem uptake of the drug. In that same study, Bromage et al. (4) discussed evidence that epinephrine itself might be able to produce some degree of segmental hypalgesia lasting several hours when applied to the spinal cord. Nevertheless, they believed that this potential effect did not contribute to the enhanced analgesia found in their volunteers given epidural morphine with epinephrine. Although the greater pain relief seen in our patients in the present study at 1 and 3 hours after the injection of hydromorphone-epinephrine (Figure 1) might be explained similarly by epinephrine induced analgesia, the major contribution of epinephrine might result from a reduction in vascular uptake of the hydromorphone that allowed enhanced dural penetration by the narcotic (10).

Robertson et al. (11) in a study of the effects of adding epinephrine to epidural fentanyl for the relief of post-cesarean section pain were able to show epinephrine prolonged the effect of fentanyl only after repeated injection. Their study was complicated by the epidural administration of epinephrine containing local anesthetic solutions prior to the administration of epidural fentanyl. Residual epinephrine effect might have affected their fentanyl-only group. Although epinephrine would be expected to reduce vascular uptake of both hydromorphone and fentanyl from the epidural space and increase the gradient for narcotic penetration into the spinal cord, thus hastening the onset of analgesia of both drugs, this effect might be harder to detect with the highly lipid soluble fentanyl that very rapidly penetrates the dura. In contrast, increasing the gradient of the less lipid soluble hydromorphone might enhance its dural penetration and, as we showed, speed the onset of its analgesic effect.

Although rare, delayed respiratory depression is the most serious adverse side effect associated with epidural opioids (4,12–16). In agreement with previous reports on epidural hydromorphone (1–3,5), delayed respiratory depression was not detected in any of our patients by the apnea monitor. The small but statistically significant increase in P_vCO_2 observed at 3 and 6 hours after the epidural dose of hydromorphone-epinephrine suggests respiratory depression in that group.

We were unable to show that the addition of epinephrine to hydromorphone changed the incidences of pruritus, nausea, and vomiting. It might be of interest to determine whether a significant difference in the incidences of these side effects would be found between the two groups if a much larger sample size were studied. In our study population, these adverse effects were antagonized effectively with small incremental doses of naloxone without decreasing analgesia (13).

In summary, the addition of epinephrine to 1.5 mg of hydromorphone administered epidurally after delivery by cesarean section provided analgesia that was faster in onset and greater in duration than that observed for plain hydromorphone. Although the presence of epinephrine resulted in a small increase in P_vCO_2, clinically significant respiratory depression was not detected in our study of 30 patients.

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1989;68:323–7

Epidural Butorphanol-Bupivacaine for Analgesia During Labor and Delivery

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HUNT CO, NAULTY JS, MALINOW AM, DATTA S, OSTHEIMER GW. Epidural butorphanol-bupivacaine for analgesia during labor and delivery. Anesth Analg 1989;68:323–7.

A double-blind, randomized, dose-response study of a combination of 0.25% bupivacaine combined with 0, 1, 2, or 3 mg of butorphanol was studied in 40 laboring parturients. The optimal dose of butorphanol combined with 8.5 to 10 ml 0.25% bupivacaine was 2 mg; with 2 mg, the duration of analgesia was significantly greater and the time to onset of analgesia significantly shorter than when no butorphanol was added, and the amount of bupivacaine could be reduced 50%. Adverse fetal effects were not observed except that of a low amplitude sinusoidal fetal heart rate pattern with doses of 3 mg butorphanol. All neonatal observations were normal. It is concluded that epidural butorphanol can be a useful and safe adjunct to bupivacaine used for epidural analgesia during labor.

Key Words: ANESTHESIA—obstetrical. ANESTHETIC TECHNIQUES—epidural. ANALGESICS—butorphanol.

Epidural injection of local anesthetics provides good analgesia for both the first and second stages of labor, with minimal risk to the mother and fetus (1,2). However, the motor block that is produced may be distressing to the parturient, may result in a prolonged second stage, and may necessitate the use of forceps for delivery (3). In addition, the sympathetic block produced is associated with a high incidence of hypotension. Epidural narcotics have been administered to parturients during labor as a means of attempting to decrease the incidence and severity of these problems. However, pain relief for the first stage of labor is problematic at best with epidural meperidine (4,5) morphine (6,7), and fentanyl (8). These drugs by themselves do not reliably provide effective analgesia for the first stage of labor in most parturients, nor do epidural narcotics reliably provide pain relief for the second stage of labor or for operative deliveries.

The limitations of both local anesthetics and narcotics alone can be overcome by administration of combinations of these drugs. Therefore, bupivacaine analgesia has been enhanced with several μ-receptor narcotic agonists including morphine (9), meperidine (10), and fentanyl (11).

Butorphanol is a lipid soluble narcotic with weak μ-receptor agonist and antagonist activity and strong κ-receptor agonism. κ-receptors appear to be involved in visceral pain modulation and, therefore, should be useful in reducing labor pain, which has a strong visceral component. Two to 4 mg of butorphanol administered epidurally provides excellent intra- and postoperative analgesia for 4 to 9 hours after cesarean delivery (12,13). The only side effect is mild somnolence. Significantly, no pruritis, nausea, vomiting, or respiratory depression have not been noted in any of the reported obstetrical studies to date. To determine the usefulness of this drug in labor, we undertook a double-blind, randomized dose-response study of epidural butorphanol combined with epidural bupivacaine for relief of pain during labor.

Materials and Methods

The protocol was approved by the Committee for the Protection of Human Subjects from Research Risks of

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the Brigham and Women's Hospital. Forty-two term multiparae who were ASA physical status I participated in the study. Only patients who planned epidural analgesia prior to their arrival in the labor and delivery unit were selected for the study. Written informed consent was obtained from the patients when they were in early labor. All parturients had large-bore intravenous catheters inserted into a peripheral vein before induction of anesthesia and were hydrated with 500–1000 ml of lactated Ringer's solution prior to the initiation of the epidural anesthesia. All patients were in active labor and had a minimum cervical dilatation of 4 cm. They all had a minimum pain score of 5 cm on a 10-cm linear visual analogue pain scale before the induction of the epidural anesthetic. Epidural catheters were inserted 2 cm at the L_2-L_3 interspace.

The patients were randomly assigned to one of four groups of 10 patients each to receive one of study drug combinations. The four groups received one of the following drug combinations: 10 ml of 0.25% bupivacaine (control group); 9.5 ml of 0.25% bupivacaine plus 1.0 mg of butorphanol (1 mg group); 9 ml of 0.25% bupivacaine plus 2.0 mg butorphanol (2 mg group); or 8.5 ml of 0.25% bupivacaine plus 3 mg of butorphanol. Patients were given 2–3 ml incremental epidural injections to a total volume of 10 ml over a period of 5 minutes. The composition of the drug solution injected into the epidural space was unknown to the person performing the epidural block and to those evaluating the response of the mother and neonate. Sensory levels were measured with the use of temperature (alcohol swab) and motor block with use of Bromage's criteria (1 = unable to move feet or knees, 2 = able to move feet only, 3 = just able to move knees, 4 = full flexion of knees and feet). Pain was assessed with use of a 10-cm linear visual analogue pain scale (0 = no pain, 10 = worst pain imaginable). Maternal vital signs were also recorded. Side effects such as pruritis, nausea and somnolence were scored as 0 = absent; 1 = mild, no treatment required; or 2 = severe, treatment needed. All observations were recorded 1, 3, 6, 9, 12, 15, 20, 40, and 60 minutes after the initial epidural injection and at 30 minute intervals thereafter until delivery. Continuous fetal heart rate monitoring was performed with either an external Doppler or an internal fetal scalp electrode. Uterine activity was also continuously monitored with a tocodynamometer. Cervical dilation and fetal descent were assessed by the obstetricians in their routine fashion.

If no signs of epidural anesthesia (pain relief, sensory or motor block) were observed with the initial epidural injection of the study drug, it was assumed that the catheter was not in the epidural space. This incident occurred in two patients (one who received no butorphanol and one who received 2 mg butorphanol). In these two patients, the epidural catheter was replaced and the patient was withdrawn from the study. Two subsequent patients were enrolled to replace these patients. Therefore, the total number of patients who were enrolled in the study was 42, but the number who completed the study and whose data were analyzed was 40, 10 in each dosage group.

After the initial period of pain relief, subsequent injection of 0.25% bupivacaine were administered as needed to produce continued analgesia.

At the time of delivery, sensory level and motor block were again evaluated and samples of umbilical arterial and venous blood and maternal venous blood were obtained for measurement of blood gas tensions. Apgar scores were recorded at 1 and 5 minutes. Early neonatal neurobehavioral assessment (Scanlon) was performed approximately 4 and 48 hours after delivery.

Non-parametric data were analyzed for statistical significance with use of the Kruskal-Wallis ANOVA, whereas parametric data were analyzed with use of a multi-group analysis of variance, with the use of Statview $512^{+\text{TM}}$ on a Macintosh™ microcomputer.

Results

Patient variables: Ten patients completed the study in each dosage group. There were no significant differences among the groups in patient height, weight, or gravidity. The duration (mean = 6.5 hours) and progress of labor were similar in all groups.

The time from first injection of the study drug to complete pain relief (mean pain score of 0) was shortened by the addition of butorphanol (Fig. 1). Complete pain relief was present in 21.3 ± 5.2 minutes when no butorphanol was added to the 0.25% bupivacaine, and in 16.5 ± 3.6 minutes in those who received 1 mg of butorphanol. There was no significant difference in the onset time between these two groups. The time to onset decreased to 6.9 ± 3.6 minutes with the addition of 2 mg of butorphanol and to 6.3 ± 3.7 minutes when 3 mg of butorphanol was used. The difference in onset times between the control group and the groups of patients given 2 and 3 mg of butorphanol was statistically significant ($P < 0.05$), although the difference in the time of onset between the 2 and 3 mg groups was not. All patients had a final sensory level of T_9-T_{10}.

The duration of complete pain relief was prolonged by the addition of butorphanol (Fig. 1). Pa-

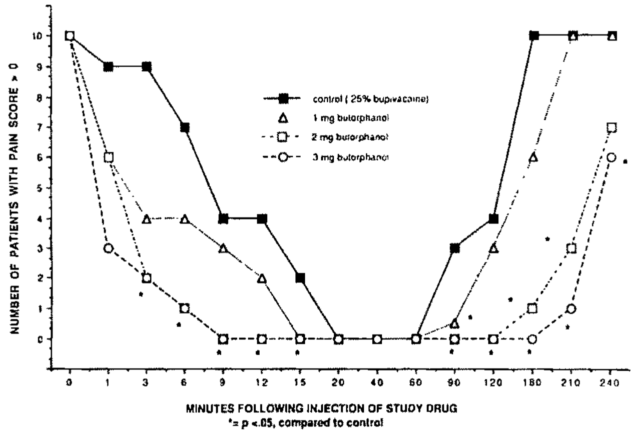

Figure 1. The number of patients with a pain score of >0 at each of the intervals after epidural injection of 0.25% bupivacaine with or without butorphanol. Analgesia was significantly more rapid in onset and longer in duration ($p < 0.05$) (asterisks) in the patients given 2 or 3 mg butorphanol than in those given 0 or 1 mg butorphanol.

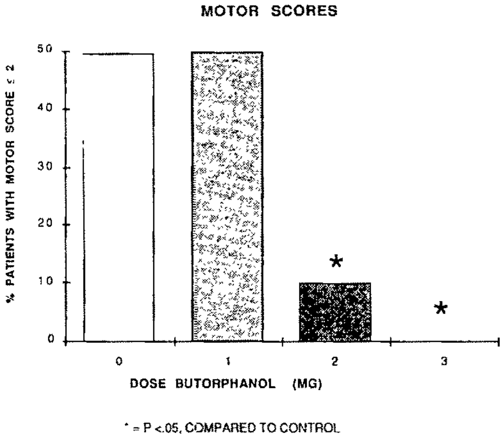

Figure 2. The percentage of patients in each study group who had profound motor block (a motor score of ≤2 on Bromage's scale) at the time of delivery. Significantly fewer of the patients given 2 and 3 mg butorphanol groups developed this degree of motor block ($P < 0.05$) (asterisks).

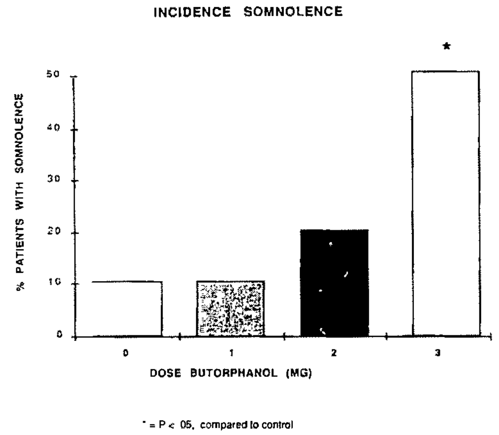

Figure 3. The percentage of patients who developed somnolence in each of the study groups. Significantly more patients given 3 mg epidural butorphanol developed somnolence ($p < 0.05$) (asterisks).

tients receiving no butorphanol had a mean duration of pain relief of 59 ± 12.3 minutes, and those who received 1 mg of butorphanol had a mean duration of complete pain relief of 67 ± 15.2 minutes. There was no significant difference in this time between these two groups. The duration of complete analgesia was increased to 137 ± 18.4 minutes with the addition of 2 mg of butorphanol, and complete pain relief lasted 220 ± 24.1 minutes with the addition of 3 mg of butorphanol. The difference in duration of pain relief between the control group and the groups of patients given 2 or 3 mg of butorphanol was statistically significant ($P < 0.02$), although the difference between the groups receiving 2 mg or 3 mg of butorphanol was not.

The total dose of bupivacaine was 43 ± 7.7 ml (107.5 mg) in the control group. There was a statistically insignificant reduction to 31 ± 12.1 ml (77.5 mg) of bupivacaine with the addition of 1 mg of butorphanol. However, with the addition of 2 mg the total dose was decreased to 20.5 ± 3.5 ml (51.25 mg), and in the 3 mg group the total dose of local anesthetic averaged 22 ± 8.6 ml (55 mg). The total dose of bupivacaine used in the groups in which 2 and 3 mg butorphanol was added to 0.25% bupivacaine was significantly less ($P < 0.01$) than that used in the control group.

The degree of motor block is illustrated in Figure 2, which represents the percentage of patients who had a dense motor block, i.e., a motor score of 1 or 2. These patients were either totally unable to move their lower extremities or could flex only their ankles. Half the patients given 0 and 1 mg of butorphanol had this degree of motor blockade. One of 10 patients given 2 mg of butorphanol had a dense motor block ($P < 0.02$, compared with control). None of the patients given 3 mg of butorphanol experienced a dense motor block ($P < 0.02$, compared with control).

The incidence of somnolence increased with the higher doses of butorphanol (Fig. 3). One patient in the control group and one in the group receiving 1 mg of butorphanol became somnolent. Two patients given 2 mg of butorphanol became somnolent, whereas half (5) of the patients given 3 mg of butorphanol became somnolent. The difference between 0 and 3 mg of butorphanol was significant ($P < 0.05$). All patients were easily aroused and no treatment was required. All maintained a respiratory rate greater than 12 throughout the study period and for 24 hours postpartum.

None of the patients developed hypotension, nausea, or pruritis.

All of the patients delivered vaginally, either spontaneously or with outlet forceps. There was no difference in the duration of the second stage of labor or in the frequency with which forceps were used in any of the groups. All patients had adequate analgesia for delivery; none required supplementation. All maternal venous gas tensions were within the normal range.

Fetal effects of butorphanol were limited to those whose mothers were given 3 mg of butorphanol. Four out of six fetuses in this group had low amplitude, benign sinusoidal fetal heart rate (FHR) tracings. This pattern began approximately 10 minutes after drug injection and resolved spontaneously over the next 25 minutes. No therapeutic interventions were necessary except in one fetus with a sinusoidal FHR that had fetal scalp capillary sampling performed, which revealed a normal pH.

There were no differences among groups in Apgar scores. All babies had Apgar scores of 7 or better at 1 minute and 9 or better at 5 minutes. Umbilical blood gas tensions were within the normal range in all neonates. No significant differences in neurobehavior scores or assessments of state were found among any of the dosage groups at 4 or 48 hours after delivery.

Discussion

The combination of epidurally administered narcotic and local anesthetic produces, in most instances, more rapid onset and longer duration of analgesia. To date, only μ-receptor agonists that are primarily involved with the mediation of somatic pain have been studied. κ-receptors are involved with the mediation of visceral pain and drugs that act at these receptors should be useful in reducing labor pain. We chose to investigate butorphanol, a strong κ-receptor agonist and a weak μ-receptor agonist-antagonist. This drug is commonly administered systemically for the management of labor pain and has been demonstrated to be quite safe when used in this fashion in larger doses than when employed in our study.

Our results demonstrate that onset of complete analgesia is more rapid with the addition of 2 or 3 mg of butorphanol to 0.25% epidural bupivacaine than it is with bupivacaine alone. Patients given 2 or 3 mg of butorphanol epidurally had a pain score of 0 in 6 or 7 minutes compared with that in 20 minutes in the control group. Although the onset of pain relief in the control group may seem excessively long, it reflects our strict analgesic criteria of a pain score of 0. Two or 3 mg of butorphanol also significantly prolonged the duration of complete analgesia from 67 ± 15.2 minutes in the control group to 137 ± 18.4 and 220 ± 24.1 minutes, respectively.

Butorphanol reduced the total local anesthetic requirements from 107.5 ± 19.25 mg in the control group to 51.25 ± 8.9 mg in the 2-mg butorphanol group and 55 ± 21.5 mg in the 3-mg group. It is likely that this almost 50% reduction in total local anesthetic dose provides the explanation for the dramatic reduction observed in the incidence of complete motor block found in our patients given 2 or 3 mg epidural butorphanol. Despite these effects on motor block, no effect on the duration of second stage of labor or the method of delivery was noted. All patients delivered spontaneously or with outlet forceps. However, it is unlikely that differences in labor outcome would be found with such a small total patient sample. Further studies are underway to evaluate the effect of this diminution of motor block on labor outcome.

In this study, the only maternal side effect demonstrated was a dose related somnolence. All of the parturients were easily aroused and required no treatment for their sleepiness. All parturients maintained a respiratory rate greater than 12 throughout the study period and for 24 hours postpartum. No apparent effect on the state of wakefulness of the neonates in the study was observed with these dosages of epidural butorphanol.

Subsequent to the completion of this study, we have administered 2 mg of butorphanol with 0.25% bupivacaine to over 150 patients. Two of these 150 patients who received butorphanol early in labor complained of dysphoria. Dysphoria is a recognized side effect of κ-opiate-receptor agonists. This reaction is common after administrations of drugs such as pentazocine, but is infrequent with butorphanol. If the reaction is severe enough to require treatment, large (0.4-mg) doses of intravenous naloxone have been reported to be effective (15).

Fetal effects from the epidural administration of butorphanol were seen when 3 mg were given to the mothers, namely a transient, low amplitude sinusoidal pattern on the fetal heart rate tracing of 4 of 10 fetuses. The pattern is also frequently seen when parturients are given butorphanol or other narcotic analgesics with κ-receptor activity, such as hydromorphone, intravenously (16,17). No adverse neonatal effects were found when laboring mothers were given epidural butorphanol. All neonates in our study had Apgar scores of 7 or better at 1 minute and 9 or better at 5 minutes. All umbilical venous and arterial blood gas tensions were within normal limits. Neurobehavioral scores were similar in all groups. Other studies have observed no neurobehavioral alterations in newborn animals and neonates whose mothers received much larger doses of intravenous butorphanol (18,19), which makes it unlikely that these smaller doses used for epidural analgesia would have observable fetal effects.

In conclusion, 2 mg of butorphanol administered with 0.25% bupivacaine appears to be the optimal dose to produce a more rapid onset and longer duration of epidural analgesia during labor with no adverse fetal or neonatal effects. Three milligrams of butorphanol does not further increase times of onset or duration of analgesia and is associated with maternal somnolence and a transient sinusoidal fetal heart tracing. Caution should be used when butorphanol is administered epidurally during early labor as the parturient may develop mild dysphoria.

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Ketamine for Intravenous Regional Anesthesia

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DURRANI Z, WINNIE AP, ZSIGMOND EK, BURNETT ML. Ketamine for intravenous regional anesthesia. Anesth Analg 1989;68:328–32.

We studied ketamine intravenous regional anesthesia of the upper extremity in volunteers using concentrations of 0.5%, 0.3%, and 0.2%. Ketamine 0.5 and 0.3% produced adequate intravenous regional anesthesia. Anesthesia was inadequate when a 0.2% concentration was used. However, although the 0.3% concentration provides complete sympathetic, sensory, and motor blockade when injected into the isolated extremity, unpleasant psychotomimetic effects after the release of the tourniquet limit the usefulness of this use of ketamine. Ketamine cannot be recommended for intravenous regional anesthesia unless these unpleasant side effects are abolished or controlled by means of pharmacologic adjuvants.

Key Words: ANESTHETICS, INTRAVENOUS—ketamine. ANESTHETIC TECHNIQUES, REGIONAL—intravenous.

The most serious complication of intravenous regional anesthesia is a toxic local anesthetic reaction when the tourniquet deflates unexpectedly during the procedure or when it is deflated intentionally at the end of the procedure to terminate the anesthetic. Indeed, cardiac arrest has resulted when the tourniquet was deflated intentionally after the completion of a short surgical procedure using intravenous regional anesthesia (1,2); and five deaths have been reported when the tourniquet suddenly deflated prematurely due to malfunction of the equipment or inadvertent release of the valve by inexperienced personnel shortly after the injection of the local anesthetic (3). The ideal agent for intravenous regional anesthesia would be one that had the requisite degree of local anesthetic activity, but without the systemic toxicity of currently used agents in the event of a sudden increase in the blood level due to tourniquet release. Such an agent has not yet been found, so the search for the "ideal agent" continues.

During early studies of the mechanism of the cardiovascular responses to ketamine, Dowdy et al. (4) demonstrated that ketamine possesses significant antiarrhythmic and negative inotropic activities, findings suggestive of intrinsic local anesthetic activity; and subsequent to these early studies, Dowdy et al. (5) also demonstrated local anesthetic activity in experimental animals. However, although these later studies indicated that ketamine produces profound motor blockade when injected epidurally and intrathecally, they were unable to demonstrate concomitant sensory blockade. However, Weber et al. (6) were able to produce a "ring block" of the finger in volunteers, and more recently Bion (7) produced surgical spinal anesthesia in humans using ketamine.

An interesting application of the local anesthetic properties of ketamine was the study by Amiot et al. (8) who used a 0.5% solution for intravenous regional anesthesia. Theoretically, ketamine might represent the "ideal agent" for intravenous regional anesthesia because sudden deflation of the tourniquet, whether deliberate or unexpected, should simply cause sedation and/or general anesthesia, rather than convulsions and/or cardiovascular depression. However, although satisfactory analgesia was obtained in 86% of their patients, this technique was limited by the fact that all of the patients become unconscious within a few minutes of tourniquet release. The present investigators believed that the theoretical advantages of ketamine for intravenous regional anesthesia are of such a magnitude that further studies were indicated to see whether lower concentrations of ketamine would provide adequate surgical anesthesia without the production of unconsciousness on release of the tourniquet.

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Methods and Materials

Fifteen healthy, young, adult volunteers, all of whom were free of cardiovascular and/or neurologic disease, were selected for inclusion in the study. The study was approved by the Institutional Review Board and was explained to each of the volunteers, all of whom then gave informed consent. The volunteers were divided into three groups, depending on the concentration of the ketamine to be utilized: Group A was to receive a 0.5% solution of ketamine, Group B a 0.3% solution, and Group C a 0.2% solution. However, the first two volunteers in Group C asked that the study be terminated prematurely because both found the tourniquet pain to be unbearable. Therefore, it was presumed that the 0.2% concentration of ketamine was insufficient to block tourniquet pain, so no additional studies were carried out using this concentration, and these two volunteers were excluded from the analysis and discussion of the data.

Prior to the initiation of each study, an intravenous infusion was started in the contralateral arm, a blood pressure cuff was applied to the same arm, and electrocardiographic (ECG) leads were applied. Then, after a heparinized plastic catheter had been inserted into a vein on the extremity to be studied, the extremity was exsanguinated with an Esmarch bandage, a double pneumatic tourniquet was applied proximal to the Esmarch bandage at the level of the mid-upper arm, the proximal cuff of the tourniquet was inflated, and the Esmarch bandage was removed. Thereupon, 0.6 ml/kg of ketamine (30–50 ml) diluted to the appropriate concentration with 0.9% sodium chloride was injected into the exsanguinated extremity.

After the injection of the ketamine, the onset of sympathetic block was monitored by recording the psychogalvanic reflex at 2-minute intervals and the onset of sensory block was determined by observing the subjective response to pinprick and cold stimulation. The onset of motor block was monitored continuously with the use of a hand-held plethysmograph (Emerson Relaxaid Stimulator, Model 91-E2X), which indicated (via a Statham force-transducer) the pressure changes evoked by repetitive ulnar nerve stimulation. Throughout the experiment, the blood pressure was monitored by a Dinamap automatic oscillometric blood pressure monitor before, during, and for 1 hour after the termination of the intravenous regional anesthesia. The ECG monitored cardiac rate and rhythm continuously throughout the study.

Each study was terminated on the successful maintenance of intravenous regional anesthesia for 1 hour, at which time the tourniquet was deflated by a cyclic deflation/inflation sequence with progressively increasing periods of deflation from 10–60 seconds to allow careful observation of the patient for signs of adverse and/or unpleasant sequelae. This observation period continued for 2 hours after deflation of the tourniquet, at which time the study was considered complete. The data obtained in this study were subjected to statistical analysis with use of a NOVA computer program. Differences were considered significant when $P < 0.05$. All values are expressed as a mean ± SE except for the demographic data, which are expressed as the mean ± SD.

Table 1. Demographic Variables

Study Groups	Mean Age Yr ± SD	Mean Weight kg ± SD	Mean Height cm ± SD	Mean BSA m^2
Group A N = 5	24.2 ± 3.0	71.0 ± 16.0	175.4 ± 15.5	1.8 ± 0.3
Group B N = 5	23.4 ± 2.2	81.4 ± 15.1	183.0 ± 8.9	2.0 ± 0.2

No statistical difference between any of the variables.

Table 2. Onset of Sympathetic, Sensory and Motor Blockade

Study Group	Sympathetic Block (Min ± SE)	Sensory Block (Min ± SE)	Motor Block (Min ± SE)
Group A N = 5	6.0 ± 0.5	9.0 ± 1.1*	16.5 ± 0.7†#
Group B N = 5	7.2 ± 0.4	7.8 ± 0.8	13.4 ± 0.7†#
Group C N = 10	6.8 ± 0.3	8.3 ± 0.6*	14.8 ± 0.7†#

*$P < 0.05$ sympathetic vs. sensory block.
†$P < 0.001$ sensory vs. motor block.
#$P < 0.001$ sympathetic vs. motor block.

Results

Table 1 indicates that the two groups of volunteers, who were all healthy, young men, were very similar demographically, there being no statistically significant difference between the two groups with respect to any of the variables. As may be seen in Table 2, sympathetic, sensory, and motor blockade occurred sequentially: in Group A, the difference in the times required for blockade of each modality were statistically significantly different from each other; whereas in Group B, which received the lower concentration of ketamine, the difference in the times

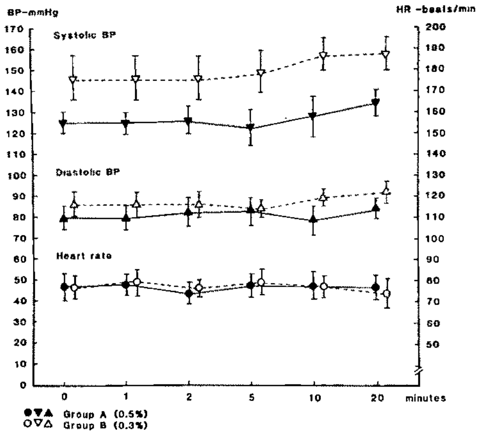

Figure 1. Blood pressure (BP) and heart rate in Groups A and B at the time of 1, 2, 5, 10, and 20 min after the release of the tourniquet. No statistically significant changes occurred in either group.

Table 3. Incidence of Complications After Deflation of Tourniquet

	Katamine Concentrations	
	Group A (0.5%)	Group B (0.3%)
Central nervous system		
Loss of consciousness	0/5	1/5
Nystagmus	5/5	5/5
Psychotomimetic effects	5/5	5/5
Other complications		
Hypersecretion	3/5	5/5
Nausea	2/5	5/5
Vomiting	0/5	2/5
Headache	2/5	1/5
Sweating	5/5	5/5
Tourniquet pain at 1 hr or less	0/5	0/5

required for sympathetic and sensory blockade were not significantly different, though the times required for full blockade of both of these modalities did significantly differ from the time required for motor blockade.

No significant changes in heart rate or blood pressure occurred during the 1 hour study period, nor were there any significant changes in these hemodynamic variables during and/or after the gradual deflation of the tourniquet (Fig. 1). During the 1 hour observation period after tourniquet deflation, the ketamine-induced signs and symptoms were varied and frequent (Table 3). Distortion of reality and/or overt hallucinations occurred in all volunteers. Although incremental doses of intravenous diazepam successfully restored normal orientation within 20 minutes, all of the volunteers considered the experience to be unpleasant and unacceptable.

Discussion

The effectiveness of ketamine as a local anesthetic for intravenous regional anesthesia is indicated in the present study by the immediate, sequential onset of sympathetic, sensory, and motor blockade after the injection of 0.3% and 0.5% ketamine intravenously into the exsanguinated, isolated upper extremity of the volunteers in Groups A and B, a sequence identical to that observed after the use of conventional local anesthetic agents. Therefore, the local anesthetic potency of ketamine appears to be almost identical to that of procaine because Bier (9) was able to obtain good intravenous regional anesthesia with concentrations of procaine as low as 0.25% in his initial reports, though 0.5% procaine hastened the onset and intensified the anesthesia. As stated earlier, Dowdy et al. (5) documented the similarities between ketamine and the local anesthetics by demonstrating that ketamine could produce reversible inhibition of the compound action potential of the stimulated frog sciatic nerve and reversible segmental paralysis when injected into the subarachnoid space of dogs. However, Dowdy (5) did not demonstrate ketamine to be capable of producing sensory blockade. Only Ahuja (10), working with rats, found intrathecal ketamine to be capable of producing analgesia, but even he found its sensory blockade to be inconsistent and of short duration.

More recently, Mankowitz et al. (11) demonstrated that 4 mg of ketamine (10 ml of a 0.04% solution) administered epidurally produced relief of pathologic pain in the lower abdomen, back, and legs in seven patients with recurrent carcinoma of the cervix. Yet, when the same investigators used the same amount of epidural ketamine for postoperative pain relief, they found the relief to be inadequate, explaining the difference in effect on the basis that "the pathways of chronic pain are very different from those of acute pain" (12). Islas et al. (13) subsequently found epidural ketamine provides good postoperative pain relief but without evidence of sympathetic, sensory, or motor blockade. They presumed that because ketamine produces lamina-specific inhibition of dorsal horn activity (14) and interacts as an agonist with opiate receptors (15,16), the selective analgesia associated with the epidural injection of ketamine was due to diffusion across the dura and into the spinal cord, a mechanism similar to that of the opioids (17). The demonstration by Fratta et al. (18) that the analgesia produced by ketamine is not reversed by nalaxone appears to refute this proposed mechanism of action, but it becomes a moot point because Ravat and his co-workers (19) in France and Ivankovich and

McCarthy (20) in the United States have reported epidural ketamine to be totally ineffective in controlling postoperative pain. However, it may be that the dosage utilized by the latter investigators was inadequate; other investigators have obtained postoperative pain relief at higher doses but only with significant systemic effects (13,21).

The results obtained in our study suggest a simple local anesthetic effect of ketamine at least when utilized for intravenous regional anesthesia. That ketamine has a local anesthetic effect is supported by the findings of Tsai (22) in monkeys and Bion (7) in humans that intrathecal ketamine can produce anesthesia of sufficient intensity to allow surgery, though in humans, at least, that the short duration of the anesthesia produced limits the usefulness of this application of ketamine (7). Because any agent utilized for intravenous regional anesthesia only provides anesthesia until deflation of the cuff, the duration of anesthesia provided by ketamine is not a limiting factor when used for this technique.

The safety of ketamine when used for intravenous regional anesthesia in terms of hemodynamic responses is also evident from our study. The heart rate and blood pressure remained unchanged for the entire 3-hour study period, even when the tourniquet was deflated (Fig. 1). Ketamine did not produce any of the usual signs of central nervous system toxicity associated with high levels of local anesthetic agents, nor did it produce unconsciousness in either concentrations. However, the occurrence of unpleasant psychotomimetic effects after release of the tourniquet even when the lower 0.3% concentration was used limits the usefulness of ketamine for intravenous regional anesthesia. Our volunteers found the dreams, hallucinations, and the distortion of body image to be unacceptable side effects of this technique. Because we made every attempt to avoid these signs and symptoms by deflating with cyclic deflation and re-inflation, it is likely that these side effects would be even greater if the tourniquet were deflated with the use of a single deflation technique. Fortunately, all of the unpleasant effects of the ketamine were fairly readily controlled by the intravenous administration of diazepam, but in spite of this, our volunteers found the experience unacceptable. Because the present study was designed to evaluate the efficacy and safety of ketamine and to determine the lowest effective dose, the subjects were not premedicated. It is possible that adequate premedication with a narcotic and/or benzodiazepine might eliminate the psychotomimetic effects of the ketamine, as is the case when used before general anesthesia with ketamine (23,24). Such studies are currently in progress at our institution.

In summary, the findings in the present study indicate that ketamine is an effective local anesthetic agent for intravenous regional anesthesia and is capable of providing complete sympathetic, sensory, and motor blockade at concentrations of 0.3% and 0.5%. Although neither concentrations produced unconsciousness after release of the tourniquet (as observed by Amiot et al. (8), sufficient ketamine gains entrance into the central circulation after tourniquet release to produce an unacceptably high incidence of unpleasant, psychotomimetic sequelae. Therefore, until future studies indicate that appropriate premedication can prevent these sequelae, ketamine cannot be recommended as the anesthetic agent of choice for intravenous regional anesthesia.

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Sixty-Six Years Ago In Anesthesia & Analgesia

Seymour, E.: Presidential address: American Association of Anesthetists. Current Researches in Anesthesia and Analgesia: 1923;2:168–172.

This address gives graphic insight into some of the problems faced by physician anesthetists in the early 1920s: economic exploitation of anesthetists by surgeons and hospitals who hired anesthetists (for whom no other way of practice was available) and then charged patients more for their anesthesia than it cost to provide it; people other than MDs and nurse anesthetists who were permitted and even encouraged to give anesthesia; inability of anesthetists to function as and to be accepted as "the medical member of the surgical team"; unreliable purity of gases and anesthetics; and, above all, the absence of strong anesthetic organizations and societies. The American Association of Anesthetists (founded in 1912) with Dr. Eleanor Seymour of Los Angeles as president, was meeting in 1923 with the Pacific Coast and California Associations of Anesthetists (both founded in 1922, at the time this address was presented). At about this same time other North American anesthesia organizations included: The New York Society of Anesthetists (formed in 1911 from the Long Island Society of Anesthetists which, in turn, was founded in 1905); the Interstate Association of Anesthetists (Ohio and Kentucky) founded in 1915; the American Society of Regional Anesthesia (1923); the Canadian Society of Anaesthetists (1921); the Southern Association of Anesthetists (1921); the Eastern Society of Anesthetists (1923); and the National Anesthesia Research Society (1919). A driving force behind creation of the last four of these organizations was the indefatigable organizer of modern anesthesia, Francis McMechan. McMechan was also guiding light in the American Association of Anesthetists, which eventually became the Association of Anesthetists of the United States and Canada in 1926 before, in 1941, becoming a part of the International Anesthesia Research Society (IARS), itself a derivative in 1925 of the National Anesthesia Research Society (NARS). In 1926 the Southern Association of Anesthetists and the Eastern Society of Anesthetists also became part of IARS. This array of names of the early anesthesia societies in North America is mind-boggling, but it reflects the difficulties inherent in forming coherent, large anesthesia societies at a time when there were only a few anesthetists spread out over a continent so huge it took five days by train to get from one coast to the other. In addition to the problems of communication and travel there was also lack of unanimity amongst those few pioneer anesthetists as to what the ultimate destiny of organized anesthesia might consist of, to say nothing of how to achieve this destiny, whatever it was. Eventually all these initial societies settled down into three large ones: the American Society of Anesthetists, founded in 1936 from the New York Society of Anesthetists; the IARS; and the Canadian Anaesthetists' Society, founded in 1943 (the original CAS disbanded in 1927 to become the Anaesthetic Section of the Canadian Medical Association). The stable three-society state of organized anesthesiology in North America lasted for several decades before gradually reverting to a multi-society specialty, a process that has substantially accelerated in recent years. The new state of multiple anesthesia societies is not based, however, on vast geography and insufficient communication as in earlier years, but, rather, on the growth of subspecialties within anesthesiology.

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Hemodynamic Effects of Mivacurium Chloride Administered to Patients During Oxygen-Sufentanil Anesthesia for Coronary Artery Bypass Grafting or Valve Replacement

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The hemodynamic effects of mivacurium chloride were studied in 54 adult cardiac patients anesthetized with midazolam and sufentanil. After baseline data were collected, a placebo (N = 9) or mivacurium was administered over 60 seconds, the latter in doses of 0.15 (N = 18), 0.20 (N = 18), or 0.25 (N = 9) mg/kg. Measurements were repeated 2, 5, and 10 minutes later. Baseline measurements were similar. A slight decrease in heart rate over time reached statistical significance in several groups including the control group. Mean arterial, mean pulmonary arterial, pulmonary arterial occlusion, and right atrial pressures and cardiac output did not change, nor did systemic and pulmonary vascular resistances and cardiac index. Besides the decrease in heart rate, the only hemodynamic change to reach statistical significance was an increase in stroke volume in patients given mivacurium 0.25 mg/kg. Significant hypotension occurred in two patients; in one, a sudden decrease in mean arterial pressure of 24% occurred 1 minute after mivacurium 0.20 mg/kg. Blood pressure was restored by ephedrine 10 mg. In the other patient, given mivacurium 0.25 mg/kg, mean arterial pressure decreased 50% from 73 to 37 mm Hg. Recovery was rapid without treatment. It is concluded that mivacurium administered in doses of 0.15 to 0.25 mg/kg over 60 seconds to cardiac patients is associated with few significant hemodynamic effects However, a small number of patients may experience significant transient hypotension when given doses greater than of 0.15 mg/kg, two times the ED95.

Key Words: NEUROMUSCULAR RELAXANTS—mivacurium.

Mivacurium chloride is an investigational nondepolarizing neuromuscular blocking drug with a short duration of action that is associated with hemodynamic stability in volunteers and healthy patients given doses up to 0.15 mg/kg as a rapid bolus over 5 to 15 seconds (1,2). Larger doses of 0.20 and 0.25 mg/kg have occasionally been associated with transient decreases in arterial blood pressure (BP) sometimes accompanied by changes in heart rate (HR) (3–5). These changes in BP and HR may be attenuated by the administration of mivacurium as a slow bolus over 30 to 60 seconds (5). The purpose of this study was to assess the hemodynamic effects of mivacurium administered in doses of 0.15, 0.20, and 0.25 mg/kg over 60 seconds to adult patients undergoing coronary artery bypass graft (CABG) or valve replacement (VR) procedures.

Methods

Fifty-four patients 22 to 82 years of age scheduled for elective CABG or VR procedures were enrolled in the

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study after an institutional approval and informed consent were obtained. All patients were ASA physical status III or IV and met New York Heart Association criteria for functional Class I, II, III or IV. Patients were excluded from the study for the following reasons: childbearing potential; a history of chronic alcoholism and/or known drug abuse; evidence of clinically significant renal or hepatic impairment; a history of asthma; recent exposure to antibiotics except penicillin, cephalosporins or tetracyclines; exposure to H1- or H2-receptor blocking drugs within 48 hours prior to anesthetic induction; exposure to antidepressants or phenytoin within 1 week of entry into the study; exposure to intravenous vasoactive or cardiotonic drugs at the time of entry into the study.

Preanesthetic medication administered 90 minutes prior to anticipated induction consisted of morphine 10 to 15 mg and scopolamine 0.4 mg intramuscularly along with lorazepam 2 to 4 mg orally. Beta-adrenergic blocking drugs, calcium entry blocking drugs, and oral or topical nitrates were continued as prescribed until the time of surgery. An intravenous infusion of balanced electrolyte solution was given in a volume equal to the fluid deficit that occurred during preoperative fasting. The patients also received purified plasma protein fraction (Plasmanate®) 500 to 1000 ml. This pre-induction loading with colloid is a standard procedure at our institution to help optimize preload and to facilitate the eventual removal of autologous blood after completion of the hemodynamic study. Initial monitoring included leads II and V_5 of the electrocardiograph (ECG) and direct radial arterial blood pressure. The ECG and peripheral arterial, pulmonary arterial, and right atrial pressures were recorded continuously with use of an Electronics for Medicine four-channel heat-sensitive paper recorder. The evoked integrated electromyogram (IEMG) of the adductor pollicis muscle after transcutaneous ulnar nerve stimulation at the wrist was recorded with use of the Puritan-Bennett/Datex® NMT 221 monitor (6). A train-of-four stimulus current at 2 Hz was delivered every 20 seconds.

Anesthetic induction included intravenous midazolam 0.2 to 0.3 mg/kg and sufentanil 0.01 to 0.03 mg while the patient breathed 100% oxygen by face mask. Tracheal intubation followed administration of succinylcholine 1 mg/kg intravenously and topical lidocaine 160 mg. Anesthesia was maintained with an infusion of sufentanil 0.0005 to 0.001 mg/minute. Ventilation of the lungs was controlled to maintain end-tidal PCO_2 at 30 to 35 mm Hg. A pulmonary artery catheter was inserted via the right internal jugular vein, and a thermistor-equipped stethoscope was placed in the esophagus.

Table 1. Study Groups

Group	N	Procedure	Dose
A1	9	CABG	Mivacurium 0.15 mg/kg
A2	9	CABG	Mivacurium 0.20 mg/kg
A3	9	CABG	Mivacurium 0.25 mg/kg
B1	9	VR a	Mivacurium 0.15 mg/kg
B2	9	VR b	Mivacurium 0.20 mg/kg
C	9	CABG	Saline 0.080 ml/kg

CABG = Coronary Artery Bypass Graft; a = aortic valve replacement (N = 5) mitral valve replacement (N = 3), aortic and mitral valve replacement (N = 1); b = aortic valve replacement (N = 7), mitral valve replacement (N = 2).

During a period of stable vital signs at least 15 minutes after tracheal intubation in the absence of surgical stimulation and after complete recovery from the effects of succinylcholine as measured by IEMG, baseline measurements of mean arterial pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP), pulmonary artery occlusion pressure (PAOP), and right atrial pressure (RAP) were made. Triplicate measurements of each variable were made and expressed as the mean value. Thermodilution cardiac output (CO) determinations were made and expressed as the mean of the values calculated from two well-formed curves with use of an American Edwards Laboratories Model COM-1 Cardiac Output Computer. Derived variables including cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated with use of standard formulae after completion of the study.

There were six groups of patients with nine patients in each group (Table 1). After baseline hemodynamic measurements, three groups of the patients undergoing CABG procedures received mivacurium 0.15 mg/kg (Group A1), 0.20 mg/kg (Group A2), or 0.25 mg/kg (Group A3). These doses approximate 2, 2.5, and 3 times its ED95 of 0.08 mg/kg during nitrous oxide-opioid anesthesia (1). The control group consisted of CABG patients who received normal saline solution 0.08 ml/kg (Group C). The patients undergoing VR procedures were given mivacurium 0.15 mg/kg (Group B1) or 0.20 mg/kg (Group B2). All injections were made slowly into a peripheral vein over 60 seconds. All measurements and calculations were repeated 2, 5, and 10 minutes after completion of the injection with the patient supine. Bladder catheterization and skin preparation were not done until all required hemodynamic data had been collected. Vasoactive and cardiotonic drugs were not administered during the study period.

Table 2. Demographic Characteristics

	Groups A1, A2, A3 N = 27	Groups B1, B2 N = 18	Group C N = 9	P Value
Age (yr)				
Mean	58	57	57	0.5139
SD	9	8	7	
Range	40–73	22–82	43–64	
Height (cm)				
Mean	173	174	172	0.8709
SD	11	9	10	
Range	152–193	156–188	152–180	
Weight (kg)				
Mean	87	79	93	0.1226
SD	20	13	14	
Range	60–135	54–106	69–114	
Body Surface Area (m^2)				
Mean	2.00	1.92	2.05	0.1614
SD	0.28	0.18	0.17	
Range	1.55–2.64	1.65–2.32	1.83–2.30	
Sex				
Female	6 (22%)	4 (22%)	1 (11%)	0.7517
Male	21 (78%)	14 (78%)	8 (89%)	
NYHA				
CLASS 1	2 (7.5%)	2 (11%)	0	0.7457
CLASS 2	12 (44%)	7 (39%)	4 (44%)	
CLASS 3	11 (41%)	9 (50%)	5 (56%)	
CLASS 4	2 (7.5%)	0	0	

Table 3. Preoperative Vasoactive Drugs

	Group A1 (N = 9)	Group A2 (N = 9)	Group A3 (N = 9)	Group B1 (N = 9)	Group B2 (N = 9)	Group C (N = 9)
Beta-Adrenergic Blocking Drugs	2	4	3	0	2	3
Calcium Entry Blocking Drugs	4	8	7	3	2	5
Nitrates	6	6	5	0	0	7

The study was unblinded beginning with the control Group C. Groups A1, A2, and A3 were entered sequentially, as were Groups B1 and B2. Patients for CABG procedures were entered concurrently with VR patients. When each patient had 95% recovery of the first response to train-of-four stimulation after mivacurium administration, pancuronium was administered to provide additional surgical relaxation. Patients were allowed to recover spontaneously from the pancuronium-induced neuromuscular block in the intensive care unit.

Summary statistics were generated by treatment group for hemodynamic variables measured at baseline and 2, 5, and 10 minutes after injection of mivacurium or saline solution. An analysis of variance (ANOVA) was performed to detect changes over time in hemodynamic variables for all groups. When statistically significant changes were found by ANOVA, contrast tests, a general form of the paired *t* test, were performed to compare the hemodynamic variables at 2, 5, and 10 minutes after injection to baseline values. The continuous-type demographic data (age, weight, and body surface area) were analyzed with use of ANOVA. The categorical demographic data (sex and New York Heart Association classification) were analyzed with the use of a modified chi-square procedure.

Results

Demographic characteristics are summarized in Table 2. There were no statistically significant intergroup differences with respect to age, sex, height, weight, body surface area, or New York Heart Association classification. Table 3 denotes the number of patients in each group receiving beta-adrenergic blocking drugs, calcium entry blocking drugs, and oral nitrates during the 12 hours prior to beginning the study. In Group B1 there were five patients who underwent aortic valve replacement, three patients who underwent mitral valve replacement, and one patient who

Table 4. Measured Hemodynamic Variables (mean ± SD)

	Group	N	Baseline	2 Min	5 Min	10 Min	ANOVA P Value
Mean Aterial Pressure (mm Hg)	A1	9	75 ± 6	73 ± 4	72 ± 4	73 ± 5	0.3625
	A2	8	72 ± 4	74 ± 4	73 ± 4	73 ± 5	0.4915
	A3	9	68 ± 3	67 ± 3	70 ± 3	71 ± 3	0.3191
	B1	9	70 ± 5	68 ± 6	69 ± 5	68 ± 5	0.2456
	B2	9	59 ± 4	62 ± 3	63 ± 3	63 ± 2	0.501
	C	9	74 ± 3	74 ± 3	74 ± 3	74 ± 3	0.8865
Heart Rate (beats/min)	A1	9	58 ± 3	55 ± 3	55 ± 2	53 ± 3	0.0002a
	A2	8	58 ± 2	56 ± 3	55 ± 2	55 ± 2	0.0873
	A3	9	61 ± 4	57 ± 3	56 ± 3	55 ± 3	0.0007a
	B1	9	61 ± 2	57 ± 1	57 ± 2	58 ± 2	0.0002a
	B2	9	59 ± 3	56 ± 3	56 ± 3	56 ± 3	0.152
	C	9	52 ± 3	51 ± 3	50 ± 3	49 ± 3	0.0032a
Mean Pulmonary Artery Pressure (mm Hg)	A1	9	21 ± 2	19 ± 2	19 ± 2	19 ± 2	0.0883
	A2	8	20 ± 2	20 ± 2	19 ± 2	19 ± 3	0.0565
	A3	8	20 ± 2	20 ± 2	20 ± 2	20 ± 2	0.8449
	B1	8	25 ± 3	23 ± 3	22 ± 3	243 ± 3	0.0569
	B2	8	20 ± 1	21 ± 1	21 ± 1	22 ± 1	0.1237
	C	9	20 ± 2	20 ± 2	21 ± 1	21 ± 1	0.6246
Pulmonary Artery Occlusion Pressure (mm Hg)	A1	9	14 ± 2	13 ± 2	14 ± 2	13 ± 2	0.6829
	A2	8	14 ± 3	15 ± 3	14 ± 3	14 ± 3	0.1562
	A3	8	16 ± 1	16 ± 2	16 ± 2	17 ± 2	0.5426
	B1	7	16 ± 3	16 ± 2	15 ± 2	16 ± 2	0.8057
	B2	8	15 ± 2	17 ± 1	17 ± 1	17 ± 1	0.1281
	C	9	15 ± 2	14 ± 2	16 ± 1	16 ± 1	0.2665
Right Atrial Pressure (mm Hg)	A1	9	10 ± 1	10 ± 1	10 ± 1	11 ± 1	0.0953
	A2	8	9 ± 3	9 ± 2	10 ± 2	10 ± 2	0.3695
	A3	9	9 ± 2	10 ± 2	9 ± 2	10 ± 2	0.6807
	B1	9	8 ± 2	8 ± 2	8 ± 2	8 ± 2	0.556
	B2	9	10 ± 1	11 ± 1	11 ± 1	11 ± 1	0.6594
	C	9	12 ± 1	13 ± 2	13 ± 1	12 ± 1	0.219
Cardiac Output (Liter/min)	A1	9	3.9 ± 0.4	3.8 ± 0.5	3.7 ± 0.4	3.6 ± 0.4	0.1556
	A2	8	5.3 ± 0.5	5.1 ± 0.5	5.1 ± 0.5	5.1 ± 0.5	0.5024
	A3	9	4.4 ± 0.5	4.7 ± 0.6	4.5 ± 0.5	4.5 ± 0.5	0.3383
	B1	9	3.7 ± 0.4	3.5 ± 0.4	3.6 ± 0.4	3.4 ± 0.3	0.3603
	B2	9	4.6 ± 0.4	4.6 ± 0.4	4.6 ± 0.5	4.7 ± 0.5	0.9199
	C	9	3.9 ± 0.3	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.2	0.6862

a = Significant change over time at the 0.05 level of significance.

underwent combined aortic and mitral valve replacement. Seven patients in Group B2 underwent aortic valve replacement whereas two patients in this group underwent mitral valve replacement. There were nine patients in the VR groups who also underwent CABG.

One patient in Group A2 was excluded from data analysis because ephedrine was administered during the 2-minute interval after mivacurium injection. Pulmonary artery catheter data were incomplete in one patient in each of the Groups A3, B1, and B2. These three patients were not included in the analysis of MPAP and PAOP, and PVR could not be calculated. In another patient in Group B1, PAOP and, therefore, PVR were unobtainable.

Summary statistics for the measured hemodynamic variables are presented in Table 4. Baseline hemodynamic measurements were similar among groups. A slight decrease in HR over time reached statistical significance in Groups A1, A3, and B1 as well as in the control Group C. There was no significant change in any other hemodynamic variable over time.

Summary statistics for the derived hemodynamic variables are shown in Table 5. In Group A3, there was an increase in SV from a control value of 75 ± 9 to 84 ± 10, 83 ± 9, and 84 ± 10 milliliters at 2, 5, and 10 minutes, respectively. There was otherwise no significant change in any other derived hemodynamic variable over time.

Among the 45 patients who received mivacurium, the magnitude of change in the hemodynamic variables over time was less than 20% except for three patients. There was a sudden 24% decrease in MAP

Table 5. Derived Hemodynamic Variables (mean ± SD)

	Group	N	Baseline	2 Min	5 Min	10 Min	ANOVA P Value
Cardiac Index (Liter/min per m^2)	A1	9	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.1584
	A2	8	2.5 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	0.4865
	A3	9	2.1 ± 0.2	2.2 ± 0.2	2.2 ± 0.1	2.1 ± 0.2	0.2756
	B1	9	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.3263
	B2	9	2.3 ± 0.2	2.3 ± 0.2	2.4 ± 0.2	2.4 ± 0.3	0.8885
	C	9	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	0.6593
Stroke Volume (ml)	A1	9	66 ± 5	68 ± 7	68 ± 5	67 ± 6	0.8636
	A2	8	92 ± 8	94 ± 10	96 ± 11	93 ± 9	0.6647
	A3	9	75 ± 9	85 ± 10	83 ± 9	84 ± 10	0.0077a
	B1	9	60 ± 6	62 ± 7	64 ± 6	59 ± 6	0.1967
	B2	9	77 ± 5	82 ± 6	83 ± 7	84 ± 7	0.168
	C	9	77 ± 4	78 ± 7	77 ± 6	78 ± 5	0.9639
Systemic Vascular Resistance (dynes·sec/cm^5)	A1	9	1500 ± 234	1529 ± 239	1451 ± 185	1527 ± 235	0.6783
	A2	8	1012 ± 118	1078 ± 119	1043 ± 111	1064 ± 121	0.3197
	A3	9	1166 ± 136	1074 ± 119	1180 ± 130	1196 ± 129	0.2556
	B1	9	1463 ± 176	1508 ± 190	1460 ± 151	1535 ± 183	0.7617
	B2	9	887 ± 71	945 ± 82	966 ± 134	966 ± 134	0.7368
	C	9	1315 ± 121	1294 ± 103	1334 ± 122	1345 ± 107	0.8498
Pulmonary Vascular Resistance (dynes·sec/cm^5)	A1	9	149 ± 23	140 ± 20	117 ± 15	142 ± 19	0.2433
	A2	8	83 ± 12	71 ± 11	78 ± 7	80 ± 8	0.3253
	A3	8	83 ± 15	67 ± 16	65 ± 14	69 ± 14	0.3316
	B1	7	194 ± 49	176 ± 45	188 ± 59	199 ± 69	0.7185
	B2	8	83 ± 11	71 ± 9	62 ± 7	75 ± 7	0.1473
	C	9	120 ± 20	100 ± 15	111 ± 15	100 ± 20	0.3481

a = Significant change over time at the 0.05 level of significance.

in one patient in Group A2 within 1 minute after completion of the injection of mivacurium 0.20 mg/kg. The change in MAP was accompanied by decreases of 8% in MPAP and 30% in RAP. Ephedrine 10 mg was administered and promptly restored the MAP to its baseline value. There were no changes in HR or in the ST-segments and no cutaneous erythema. Although hemodynamic variables returned to baseline values at 2 minutes, the data from this patient were excluded from the analysis because of the circulatory effects of ephedrine.

A similar hypotensive episode occurred in one patient in Group A3. About 30 seconds after completion of the injection of mivacurium 0.25 mg/kg, MAP decreased from 73 (BP 120/50) to 37 (49/30) mm Hg, a decrease of 50%. There was a simultaneous decrease in MPAP from 27 to 23 mm Hg, and RAP decreased from 8 to 7 mm Hg. The hypotensive episode was brief and did not require treatment. Mean arterial pressure measured 41, 64, and 71 mm Hg at 1, 1.5, and 2 minutes after completion of the mivacurium injection, respectively. There was no change in HR or ST-segments. Cutaneous erythema was absent. The hemodynamic data from this patient were included in the analysis.

HR in another patient in Group A3 decreased from 91 beats/min at baseline to 72, 72, and 70 beats/min at 2, 5, and 20 minutes, respectively. This decreased HR did not require treatment.

Discussion

Our finding of few circulatory changes was confirmed by another study in healthy patients using smaller bolus doses of mivacurium of 0.10 and 0.15 mg/kg (2). The average MAP and HR for the groups did not change significantly from baseline over 5 minutes. However, MAP in 5 of 18 patients decreased 15 to 21% with a concurrent decrease in HR of 10% or less.

Likewise, our finding of brief hypotension in two patients agrees with the findings of other investigators. Administered as a rapid bolus over 5 to seconds to volunteers and healthy patients, mivacurium in doses of 0.20 and 0.25 mg/kg has been associated with an average decrease in BP of 25% and an increase in HR of 25% (3), an average decrease in MAP of 19% without a change in HR (4), and a decrease in MAP of 13 to 18% without an accompanying HR change (5). In the latter study, plasma histamine concentrations increased above baseline at 2 minutes by an average of 131 and 154% with the 0.20 and 0.25 mg/kg doses, respectively. Plasma histamine concentrations were two to four times baseline values in several patients with above-average decreases in MAP associated with facial erythema. A second rapid bolus injection of mivacurium caused a much smaller decrease in MAP of 2 and 8% at 0.20 and 0.25 mg/kg, respectively. Furthermore, the average decreases in MAP were only 10 and 7% when these two doses of mivacurium were administered slowly over 30 seconds. This evidence points to histamine release as the probable mechanism of mivacurium-induced hypotension. However, none of the patients in our study, including the two patients who developed clinically significant hypotension after mivacurium, had any other clinical signs of histamine release such as cutaneous erythema or bronchospasm.

Because the reduction in MAP in our two patients was so precipitous and recovery so rapid, hemodynamic data collection was incomplete. There was insufficient time for determination of CO and measurement of PAOP. Therefore, SVR and PVR could not be calculated. No samples for determination of plasma histamine concentrations were drawn. Therefore, evidence of mivacurium-induced histamine release in these cases is circumstantial. Future protocols should include the determination of baseline and post-injection plasma histamine concentrations to further elucidate the cause of hypotension should it occur after injection of mivacurium.

To minimize the risk of histamine-induced vasodilation in our patients with cardiac disease, mivacurium was injected peripherally over 60 seconds. Central administration of drugs with histamine-releasing properties, such as protamine, has been associated with higher plasma histamine concentrations than peripheral administration (7). Although prior administration of histamine antagonists has been shown to attenuate d-tubocurarine-induced hypotension (8), we chose to avoid H1- and H2-receptor blocking drugs in our clinical trial so that any histamine released by mivacurium might be reflected in circulatory changes. We did not want to create a false sense of security about the lack of circulatory changes with mivacurium by antagonizing the effects of histamine release. On the other hand, we believed that straightforward measures such as slow peripheral injection of mivacurium to prevent histamine from being released in the first place were justified.

The saline solution control group was an important part of this protocol to unmask any circulatory changes caused by the experimental design or mechanical ventilation of the lungs. For example, on the basis of a study with fentanyl (9), it was hypothesized that HR slowing might occur while the hemodynamic data were collected during anesthesia with a sufentanil infusion in the absence of surgical stimulation. This effect of opioids on HR would be unrelated to mivacurium administration and could conceivably lower BP and CO. Such a decrease in HR was documented in both the saline solution control and mivacurium-treated groups. Because HR decreased in several groups over time whereas CO remained unchanged, it follows that calculated SV would increase. This increase in SV reached statistical significance in Group A3.

This protocol was designed to minimize the effects of the anesthetic technique on the circulation. Except for the patient who was excluded from data analysis, intravenous vasoactive and cardiotonic drugs were not administered until all hemodynamic data had been collected. Prehydration with both colloid and crystalloid solutions increased preload and maintained CO and BP to obviate the need for vasopressors during the study period. A sufficient time interval was permitted before control measurements were obtained to allow HR and BP to return to normal after succinylcholine administration, laryngoscopy, and tracheal intubation. The patients were not stimulated in any additional way until all required data had been collected. Mechanical ventilation of the lungs was instituted in advance of all hemodynamic measurements. Sufentanil was chosen for its hemodynamic stability (10). Anesthetic drug concentrations were established prior to injection of the study drug. It has been shown that background opioid anesthesia minimizes, whereas potent inhaled drugs enhance the circulatory effects of muscle relaxants (11–13).

Traditional mechanisms by which nondepolarizing neuromuscular blocking drugs exert their hemodynamic effects are histamine release, ganglionic blockade, vagolytic, and sympathomimetic effects (11–17). These effects usually occur within a 10-minute period and tend to parallel the onset of neuromuscular blockade. Hemodynamic data collected over this period most likely reflect changes due to these mechanisms. Therefore, an interval of 10 minutes for data collection is commonly utilized to uncover any changes caused by mivacurium.

The doses of mivacurium employed in this study are quite large. In the presence of opioid anesthesia, the ED95 of mivacurium has been variously reported (3,18–20) as 0.07, 0.075, 0.09, and 0.12 mg/kg in preliminary neuromuscular studies. In the most extensive study published to date (1), this value was found to be 0.08 mg/kg. Therefore, the doses that we selected represent approximately 2, 2.5, and 3 times the ED95. There have been no reports of significant decreases in BP or other circulatory changes when mivacurium was administered in doses of 0.15 mg/kg or less. Because 0.15 mg/kg represents two times the ED95 of mivacurium, larger doses of 0.20 and 0.25 mg/kg are probably unnecessary and may contribute to hemodynamic instability at least in cardiac patients.

This study shows that mivacurium administered as a slow bolus has no statistically or clinically significant effect on measured or calculated hemodynamic variables at a dose twice its ED95 and minimal effects at higher doses of 2.5 and 3 times the ED95. However, a small number of patients may experience significant transient hypotension at these higher doses. The combination of this absence of circulatory effects at clinically relevant doses and its short duration of action makes mivacurium a potentially useful drug for patients with coronary or valvular heart disease and limited cardiac reserve undergoing short operations, such as direct laryngoscopy, mediastinoscopy, or laparoscopy. It might also be a useful alternative to succinylcholine for tracheal intubation. On the basis of the cardiovascular profile developed in our study, there seems to be little reason to use doses greater than 0.15 mg/kg, two times the ED95, in the management of such patients.

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A Computerized Anesthesia Database

Paul L. Strauss, MD, and Herman Turndorf, MD

STRAUSS PL, TURNDORF HT. A computerized anesthesia database. Anesth Analg 1989;68:340–3

The collection of anesthesia related information in an organized fashion and the subsequent analysis of the data assist in the maintenance of quality anesthesia care. We have created and implemented a computerized anesthesia database that utilizes an IBM personal computer. We are now able to easily and accurately monitor the anesthesia practices of our large university anesthesia program. We recommend the wide adaptation of systems such as ours to all departments, from the small private hospital to the large university center.

Key Words: RECORDS, ANESTHESIA—computers. STATISTICS—computers.

The collection of anesthesia related information in an organized fashion and the subsequent analysis of the data assist in the maintenance of quality anesthesia care. These data include such things as the number, type, location of anesthetics administered, and a detailed description of complications. Acquiring and the statistical analysis of these data have proven to be a difficult task.

Manual data collection systems have been used but generally are unwieldy and are open to human errors in data entry, completeness, and analysis. Rovenstine (1) in 1934, well before the widespread use of computers, developed a punch card system for data collection in the operating room. This journal was one of the first publications that presented an organized record collection system. It stressed the need for widespread adoption of record collection systems and their importance in patient care.

Hospital mainframe computers have been used for data collection and analysis. Bashein and Barna (2) in 1985 discussed a computerized database using a mainframe computer that provided a case record collection system. The creation of a computerized system using the hospital mainframe, a project that would be exceedingly complicated, would be very time and effort consuming for most anesthesia departments. Because these are large multiuser systems, many limitations and problems would occur in the implementation and development of a hospital mainframe data collection system. To create or change program segments or data formats would be slow, costly, and usually subordinate to other institutional priorities.

In 1981 IBM introduced the personal computer. It has brought the power of computerization to a larger and more diverse spectrum of users. Every anesthesia department and most individual anesthesiologists are discovering the capabilities of the personal computer. We have designed a personal computer-based anesthesia record collection system to help manage a department of 65 attendings, 55 residents, and 30 CRNAs covering three hospitals in which more than 30,000 anesthetic procedures are done annually.

Methods and Materials

Our hardware requirements included an IBM compatible personal computer with at least 512K of RAM, a hard drive with a minimum of 20MB, and a printer. A graphic or color monitor adapter, an 80286 or 80386 processor, though optional, enhance the system. The core of our system is a Dell Corporation 80386, 16 HZ personal computer clone with one megabyte of RAM, 70 megabyte hard drive, and an EGA monitor. A commercially and widely used relational database, DBase III + and two enhancement products, Relational Report Writer and Dgraph for Dbase, were used to write the system. With the configuration as described, the cost was less that $5000. As computer prices decrease, the investment for hardware components may get as low as $1500. Though we used an

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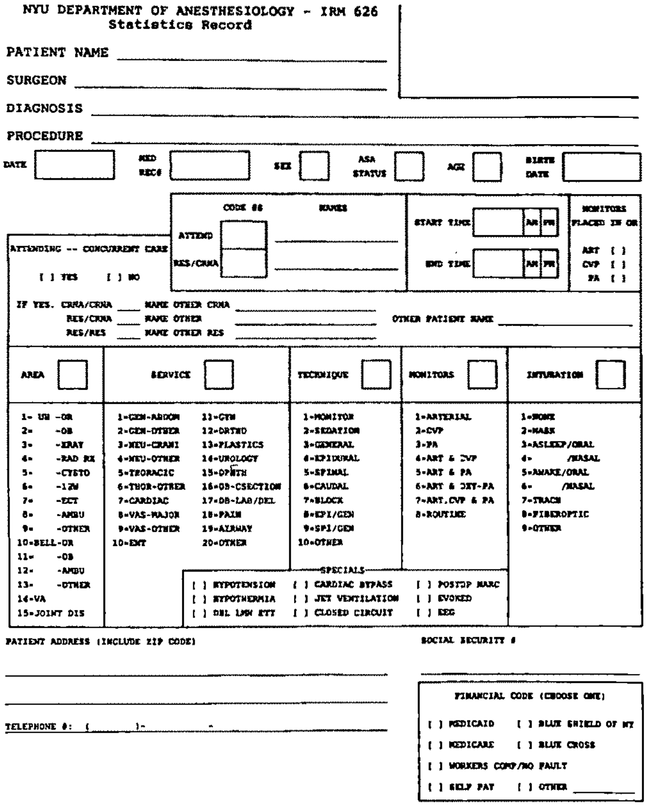

NYU DEPARTMENT OF ANESTHESIOLOGY - IRM 626
Statistics Record

PATIENT NAME ______
SURGEON ______
DIAGNOSIS ______
PROCEDURE ______

DATE ☐ MED REC# ☐ SEX ☐ ASA STATUS ☐ AGE ☐ BIRTH DATE ☐

ATTENDING -- CONCURRENT CARE
[ ] YES [ ] NO

CODE #S NAMES
ATTEND ☐ ______
RES/CRNA ☐ ______

START TIME ☐ AM PM
END TIME ☐ AM PM

MONITORS PLACED IN OR
ART [ ]
CVP [ ]
PA [ ]

IF YES. CRNA/CRNA ___ NAME OTHER CRNA ______
RES/CRNA ___ NAME OTHER ______
RES/RES ___ NAME OTHER RES ______
OTHER PATIENT NAME ______

AREA ☐	SERVICE ☐		TECHNIQUE ☐	MONITORS ☐	INTUBATION ☐
1- UH -OR	1-GEN-ABDOM	11-GYN	1-MONITOR	1-ARTERIAL	1-NONE
2- -OB	2-GEN-OTHER	12-ORTHO	2-SEDATION	2-CVP	2-MASK
3- -XRAY	3-NEU-CRANI	13-PLASTICS	3-GENERAL	3-PA	3-ASLEEP/ORAL
4- -RAD RX	4-NEU-OTHER	14-UROLOGY	4-EPIDURAL	4-ART & CVP	4- /NASAL
5- -CYSTO	5-THORACIC	15-OPHTH	5-SPINAL	5-ART & PA	5-AWAKE/ORAL
6- -12W	6-THOR-OTHER	16-OB-CSECTION	6-CAUDAL	6-ART & [illegible]-PA	6- /NASAL
7- -ECT	7-CARDIAC	17-OB-LAB/DEL	7-BLOCK	7-ART,CVP & PA	7-TRACH
8- -AMBU	8-VAS-MAJOR	18-PAIN	8-EPI/GEN	8-ROUTINE	8-FIBEROPTIC
9- -OTHER	9-VAS-OTHER	19-AIRWAY	9-SPI/GEN		9-OTHER
10-BELL-OR	10-ENT	20-OTHER	10-OTHER		
11- -OB					
12- -AMBU					
13- -OTHER					
14-VA					
15-JOINT DIS					

SPECIALS
[ ] HYPOTENSION [ ] CARDIAC BYPASS [ ] POSTOP NARC
[ ] HYPOTHERMIA [ ] JET VENTILATION [ ] EVOKED
[ ] DBL LMN ETT [ ] CLOSED CIRCUIT [ ] EEG

PATIENT ADDRESS (INCLUDE ZIP CODE) ______
SOCIAL SECURITY # ______
TELEPHONE #: ( )- -

FINANCIAL CODE (CHOOSE ONE)
[ ] MEDICAID [ ] BLUE SHIELD OF NY
[ ] MEDICARE [ ] BLUE CROSS
[ ] WORKERS COMP/NO FAULT
[ ] SELF PAY [ ] OTHER ______

Figure 1. Information collection sheet.

IBM personal computer and the relational database Dbase, other personal computers such as the MacIntosh and other relational database software can be used as well.

An information sheet was designed to collect data into the database (Fig. 1). This sheet is used to collect patient name, sex, age, ASA physical status, surgeon, diagnosis, procedure, start and end time, all of which are hand written on the sheet. Anesthesia personnel and five information fields including anesthetic area, surgical service, anesthetics used, monitoring, and intubation techniques utilize code numbers rather than written format for data entry. These fields are organized into broad and useful subgroups. A total of 22 data fields are collected. Additional information for billing is also included. Patient address, telephone, and social security number and financial code are entered at the bottom of the sheet. The incorporation of both anesthesia and billing information has minimized paper work and increases completion compliance. Completion of the record takes about 35–40 seconds.

At the start of every day, information sheets from the previous day are collated by the secretarial staff. One day of information (100–150 records) takes 2 hours to enter. The main data entry screen is a reproduction of the information sheet. This markedly speeds data entry and improves accuracy. Prompts for completeness and correctness of patient data are made by the program before data are entered into the database. Concomitant service and daily reports are generated daily, which are utilized by the secretarial and billing services to assure collection of all records and to assist in billing. Monthly summary, annual, and individual physician reports are generated on a predetermined schedule. Special ad hoc reports can be generated on request.

Backup of patient data is done weekly by the secretarial staff. After the proper selection from the menu, the records since the prior backup are copied onto floppy disks. The program checks for adequate diskspace on the backup floppy before completing the backup procedure. The program will request a new floppy disk and format the disk if necessary.

Because all programs and program codes are in our possession and written by a computer literate member of our staff, modification or change of program formats, data, or reports has been done quickly and easily during program development. Installation of the program requires copying eight files onto the hard drive from a single floppy disk. The computer must have the two commercially available programs already installed for the system to function. Expansion of the database to include the monitoring of complications is planned for the future.

Discussion

Our intent was to design a sophisticated data management system to be operated by personnel with minimal knowledge of computers. The task was particularly difficult because of the size and complexity of our department. Prior to implementation, operating room schedules, billing records, and daily operating room logs were kept separately and correlations were done manually. They provided us with very limited and inaccurate information that took days to weeks to aggregate. The operating room statistics provided us only with the number of cases broken down by month and surgical service. Our secretarial staff manually sifted through the anesthesia records and provided a monthly report by anesthetic technique (general, regional, local). This method was fraught with the inaccuracies of manual data collection. It depended on the deciphering of individual anesthesia records and the completeness of collection of all of these records. It was not able to manage large amounts of information. Our department covers many anesthetic locations, and data were not being collected in a uniform manner in the various locations. The nonuniformity of information from the various hospitals prevented the accurate aggregation of information.

Our billing service attempted to provide departmental demographic statistics. The billing system database provided us with accurate information but did not contain all the information we believed was important. The focus and orientation of the billing service are different from the needs of patient care data and could not provide us with the information we believed necessary. The billing system, even though computerized, was unable to provide us with reports on a timely schedule because of its other responsibilities.

The solution to our problem was to design a system by a computer literate member of our anesthesia staff from the ground up. This has provided us with a useful, flexible system that has evolved over the 6 months since its inception. Our anticipated departmental needs have changed with the actual implementation of the system. For example, the name of the surgeon was added to the database. As a result, we were able to analyze utilization of operating room time and provide our surgical colleagues with their case information. Times at which operations started and ended and duration of anesthesia were secondarily added to provide our billing service with a secondary check on billing services.

The custom designed information sheet was created with the use of a commercially available form development program. The information sheet has undergone 18 revisions to date as our system has evolved and our needs changed. It was important to combine information for billing and departmental statistics into a single form to minimize paper work and increase completion compliance. The use of subgroups and code numbers speeds up data entry and begins data analysis at the earliest level. The personnel performing the anesthetic categorize the patients. This eliminates data inaccuracy created by interpretation of data by secretarial staff.

Our "turn-key" system can be mastered in a single 1 hour training session. The user is presented with a series of screens and choices to operate the system. Using code numbers makes data entry faster, simpler, and far more accurate than typing each entry. Errors due to illegible handwriting are minimized by using numerical entries.

The departmental daily report allows us to monitor the actual number and type of anesthetics delivered. This report identifies the patient with the diagnosis, procedure, anesthesiologists, anesthetic location, and technique, as well as monitoring and intubation techniques. One of the three members responsible for scheduling can review the types of cases to be done and the attendings and residents that have been assigned over the previous days. The printed operating room schedule does not accurately contain the actual attending and resident case assignments. As in all institutions, during the course of the day, many changes in room assignments and in attending and resident coverage are made. The daily schedule contains all information as it actually occurred. With our timely data entry input on the following day, the availability of the daily report has improved case distribution. It acts as a form of communication between the three members of the scheduling committee.

The daily report to the billing service identifies the secondary anesthesiologist as a resident or nurse and marks overlapping coverage. With continual changes in reimbursement schedules and Medicaid laws, it was important to our billing service to identify when attendings were simultaneously supervising residents or nurse anesthetists. Data on the duration of anesthesia and surgery are forwarded to the booking department as a means for improving utilization of operating room time. Patients given epidural narcotics are automatically enrolled into our acute pain service.

Monthly summary reports are provided for attendings, residents, and CRNAs broken down by surgical service and location, anesthetic techniques, monitors used, and intubation technique. Data on the frequency distribution of attending resident and attending nurse coverage are also created. This permits us to easily equalize case experience. It ensures that all residents work with all attendings during their training.

The annual report provides residents with their yearly case summary (pink sheets) for the American Board of Anesthesiology (ABA). This report is more accurate than the individual logs kept by residents. This information, also available to program directors, allows timely modifications of and improvements in the resident training program. During training, residents can survey their experience and tailor it to their particular interests. Inequalities in individual case experiences or major program weaknesses are easily identified on a timely basis. Residents have now become compulsive in their information sheet completion, knowing this information is utilized in the annual report to the ABA.

Our computerized database has improved our departmental quality assurance program. The daily schedule is examined for any unusual combination of anesthetic technique, monitoring, airway management, especially in peripheral locations away from the main operating rooms. These cases can be further investigated to determine whether any problems occurred intraoperatively. The ASA physical status and age profiles can be studied from each anesthetic location. In peripheral areas such as the cystoscopy suite and the ambulatory surgery area, we like to limit the number of patients with an ASA physical status greater than III and schedule them in the main operating rooms. The database identifies increases in the percentage of these higher risk patients.

We did not include in our system a specific field for complications. A single nonspecific field that indicates the occurrence of any complication would be too broad, would not provide useful information, and would not be accurately completed. The hundreds of codes necessary for all the many possible complications would be too complicated to be filled out accurately and without omissions. We are currently categorizing complications as in the other fields. It has been far more difficult because of the diversity of anesthetic complications.

The database has enhanced our clinical research program. Specific patient groups can easily be identified for retrospective or prospective clinical projects. The database facilitates data collection, and statistical analysis ad hoc reports are created to provide collated reports on the basis of specific data fields. Subsequently, these charts can be obtained for retrospective analysis. We are currently performing a spinal headache survey. The database has identified and provided us a with a random sample of patients given spinal anesthetics. A phone and mail survey is being conducted to determine the incidence, duration, and predictors of post-spinal headaches.

In summary, we describe a computerized anesthesia data collection system utilizing an IBM personal computer. We have seen the benefits of this system in our practice and the simplicity of its implementation. We recommend the widespread use of systems such as the one we have used so successfully.

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ANESTH ANALG
1989;68:344–9

Effect of Anesthetic Induction Agents on Cardiovascular Neuroregulation in Dogs

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PRIANO LL, BERNARDS C, MARRONE B. Effects of anesthetic induction agents on cardiovascular neuroregulation in dogs. Anesth Analg 1989;68:344–9.

The goal of this study was to examine the hypothesis that intravenous anesthetic induction agents alter neuroregulation of the cardiovascular system. Additional goals were to investigate this in an animal model devoid of other drug effects. Healthy mongrel dogs had arterial catheters inserted and pneumatic occluders positioned around the thoracic aorta and inferior vena cava. After 10 to 14 days of recovery, neurocirculatory control mechanisms were assessed in the absence of anesthesia by recording changes in the RR interval of the electrocardiogram in response to alterations in systolic arterial pressure. Systolic pressure was manipulated over a range of 65 to 200 mm Hg by random occlusion of either the inferior vena caval (hypotension) or aortic (hypertension) occluders. The animals were then given bolus doses of either thiopental (20 mg/kg), diazepam (2 mg/kg), ketamine (5 mg/kg), or etomidate (1.2 mg/kg) on separate days and in random order. The arterial pressure alterations were repeated 3, 10, and 20 minutes after the drugs were given. Regression curves were calculated expressing the slope relation between RR interval and systolic pressure at awake control and each time point after drug administration. The responses were compared with control by repeat measures analysis of variance. Thiopental significantly decreased this slope relation for 10 minutes. Diazepam decreased this slope at 3 minutes only. Ketamine, like thiopental, decreased this slope for 10 minutes. Following etomidate, the slopes were similar to control. We conclude that thiopental, diazepam, and ketamine impair neurocirculatory control capabilities. The effect of diazepam is only transient, whereas that of thiopental and ketamine is longer, and etomidate does not affect these reflexes.

Key Words: ANESTHETICS—INTRAVENOUS: thiopental, ketamine, diazepam, etomidate. REFLEXES—baroreceptor. INDUCTION—anesthesia.

Homeostasis of the cardiovascular system is achieved by a complex network of neurocirculatory reflexes, some of which are well defined and some of which remain to be delineated (1–7). The function of neurocirculatory reflexes can be altered by pathophysiologic states (8–10) as well as pharmacologic interventions. In the latter category are anesthetics that definitely affect these homeostatic mechanisms. General anesthetics (11–15), intravenous anesthetics (16–20), and regional anesthetics (21) have all been studied in this regard. However, no systematic investigation has been performed relative to the question of how intravenous anesthetic induction agents affect this important physiologic function. More important, most of the information we have on the effects of intravenous drugs was obtained using experimental designs in which the drug being studied was given in addition to other drugs so that interpretation of results is difficult. Furthermore, in attempting to compare drugs, it is often necessary to compare results from different experimental models. The present study was designed to determine whether intravenous anesthetic induction agents alter neurocirculatory control mechanisms. The goal was to investigate this in a conscious chronically instrumented animal model so as to be able to observe the pure drug effects without the confounding background of other drugs, and then to study the same dogs when intravenous induction agents were given.

Methods and Materials

Healthy mongrel dogs of either sex, weighing 20 to 30 kg, were studied. Under endotracheal halothane and

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nitrous oxide/oxygen anesthesia, a left thoracotomy was performed in the 4–5 interspace. Pneumatic occluders (R.E. Jones, Silver Springs, MD) were loosely positioned around both the thoracic descending aorta distal to the left subclavian artery and the thoracic inferior vena cava. The internal mammary artery was cannulated with Tygon tubing and the catheter advanced into the proximal subclavian artery to monitor arterial pressure. The arterial catheter and occluding devices were routed through the 6–7 intercostal space and then subcutaneously, and exteriorized between the scapulae. The thoracic incision was closed, the chest was evacuated with suction until a seal had been obtained, and the suction tubing was removed. The animals recovered for 10 to 14 days. During this time, the patency of the arterial catheter was maintained with flushes of 1000 unit/ml of heparin solution, and the animals were trained to lie quietly awake on the experiment table on their right side.

Four drugs were randomly studied on separate days in each animal. An interval of at least 48 hours was allowed for recovery between experiments. The dosages used for the study were as follows: thiopental 20 mg/kg, diazepam 2 mg/kg, ketamine 5 mg/kg, and etomidate 1.2 mg/kg.

Experiments were performed after the animals had fully recovered from the implantation surgery and had learned to lie quietly awake on the experiment table breathing 100% oxygen. Oxygen was administered to obviate the potential effects of hypoxic chemoreceptor reflexes on the responses being measured. Oxygen was given using a comfortably fitting, conical-shaped canine anesthesia mask connected to an Ayres T–Jackson-Rees breathing system. This was well tolerated in a conscious animal after minimal training. A calm awake control state was manifested by a normal heart rate of <100 beats/minute, as well as calm overall animal behavior. In random sequence, either the inferior vena caval or aortic occluder was then inflated. Inferior vena caval occlusion decreased venous return and subsequently systolic pressure, thereby inducing a reflex increase in heart rate. Aortic occlusion elevated systolic pressure, producing a reflex slowing of heart rate. Use of the occluders allowed manipulation of systolic blood pressure to occur over a range of 65 to 200 mm Hg. The subsequent alteration in the pulse rate, as reciprocally indexed by the RR interval, allowed assessment of the sensitivity of the neurocirculatory reflex loop. A plot of the relation between the RR interval (in milliseconds) and systolic pressure (in millimeters of mercury) established a control slope relation for that particular animal on that particular day. This technique has been previously described (8,22). Drug studies were not performed unless the correlation coefficient between RR interval and systolic pressure was ≥0.7 during awake control conditions. Subsequently, the drug being studied was administered as a bolus over 30 to 45 seconds. Blood pressure manipulations with the occluders were repeated 3, 10, and 20 minutes after drug administration while the animals continued to breath oxygen spontaneously.

The relation between RR interval and systolic blood pressure for each awake control response and each postdrug response was analyzed by least squares regression analysis to arrive at a correlation coefficient, slope, and intercept for that response. The regression curves for the postdrug responses were then compared with the awake control curves, employing repeated measures analysis of variance (23). If this analysis indicated that a statistically significant change had occurred, further analyses were performed using a Tukey Range test (23) to identify statistically significant changes at the specific time intervals after drug administration.

Results

Control data and data obtained after each of the four drugs had been given are summarized in Table 1. The control slope relation in the thiopental group was 5.4 ± 0.7 ms/mm Hg. This was statistically significantly depressed for 10 minutes after drug administration. By 20 minutes, it had returned to control levels. The preocclusion heart rates and blood pressures after thiopental were, with a few exceptions, not significantly different from those obtained in the awake control state.

The control slope relation in the diazepam group of animals was 8.6 ± 1 ms/mm Hg. Diazepam significantly decreased this relation at 3 minutes after drug administration. Heart rates and blood pressures before occlusions following diazepam were not significantly different from those observed in conscious control dogs.

The baseline slope relation in the ketamine group was 3.5 ± 0.42 ms/mm Hg. This was significantly depressed for 10 minutes following drug administration. The preocclusion heart rates and blood pressures were significantly elevated at all time points after ketamine.

During the awake control period, the slope relation before etomidate administration was 6 ± 1.5 ms/mm Hg. This relation was not significantly altered after etomidate administration. The preocclusion heart rates were significantly decreased after etomi-

Table 1. Regression/Hemodynamic Data

	Conscious Control	3 Minutes After Drug	10 Minutes After Drug	20 Minutes After Drug
Thiopental				
m	5.4 ± 0.7	1.6 ± 0.4*	1.9 ± 0.5*	6.1 ± 1
r	0.83 ± 0.03	0.65 ± 0.06*	0.66 ± 0.05*	0.79 ± 0.03
HR	88 ± 5	117 ± 13*	103 ± 7	90 ± 10
SBP	133 ± 4	124 ± 5	118 ± 5*	116 ± 10
n	9	9	9	6
Diazepam				
m	8.6 ± 1	2.2 ± 0.5*	6.5 ± 1.5	10 ± 1.6
r	0.88 ± 0.02	0.64 ± 0.09*	0.85 ± 0.02	0.82 ± 0.04
HR	83 ± 6	95 ± 5	84 ± 7	77 ± 6
SBP	137 ± 4	142 ± 9	133 ± 4	128 ± 5
n	10	10	10	7
Ketamine				
m	3.5 ± 0.42	0.95 ± 0.11*	1.2 ± 0.2*	1.9 ± 0.4
r	0.82 ± 0.03	0.82 ± 0.04	0.77 ± 0.08	0.83 ± 0.06
HR	84 ± 3	168 ± 10*	169 ± 13*	144 ± 8*
SBP	141 ± 3	166 ± 7*	171 ± 6*	159 ± 9*
n	10	10	10	7
Etomidate				
m	6 ± 1.5	9.9 ± 2.4	9.9 ± 2	5.6 ± 2.1
r	0.87 ± 0.02	0.69 ± 0.12	0.83 ± 0.04	0.68 ± 0.08
HR	82 ± 7	72 ± 5*	66 ± 5*	65 ± 5*
SBP	132 ± 5	122 ± 5*	125 ± 5	134 ± 7
n	9	9	9	7

Correlation coefficients (r) and slope values (m) for the RR interval (ms)/systolic blood pressure (mm Hg) relation in awake control dogs and after drug administration. Also shown are the data for heart rate (HR) in beats/minute, systolic blood pressure (SBP) in mm Hg, and number of animals (n) included at that time for the four drugs studied. Values are means ± SEM. An asterisk indicates a significant ($P < 0.05$) difference between the awake control responses and those after drug administration.

Table 2. Arterial Blood Gas Tensions and pH

	Conscious Control	3 Minutes After Drug	10 Minutes After Drug	20 Minutes After Drug
Thiopental				
pH	7.42 ± 0.01	7.32 ± 0.01*	7.33 ± 0.01*	7.35 ± 0.01*
PCO2	38 ± 2	51 ± 3*	50 ± 3*	47 ± 2*
PO2	396 ± 31	370 ± 23	387 ± 21	392 ± 29
Diazepam				
pH	7.41 ± 0.01	7.40 ± 0.01	7.41 ± 0.01	7.42 ± 0.01
PCO2	37 ± 1	40 ± 1*	39 ± 1	37 ± 1
PO2	320 ± 21	372 ± 27	379 ± 30	349 ± 39
Ketamine				
pH	7.42 ± 0.01	7.38 ± 0.01*	7.40 ± 0.01*	7.41 ± 0.01
PCO2	37 ± 2	41 ± 1*	41 ± 2*	38 ± 1
PO2	327 ± 29	334 ± 31	302 ± 39	285 ± 40
Etomidate				
pH	7.41 ± 0.01	7.34 ± 0.01*	7.41 ± 0.01	7.42 ± 0.01
PCO2	40 ± 1	46 ± 2*	39 ± 2	37 ± 2
PO2	324 ± 26	354 ± 22	369 ± 21	374 ± 25

Arterial blood gas tensions and pH during awake control and 3, 10, and 20 minutes after drug administration. Values are means ± SEM. An asterisk indicates a statistically significant ($P < 0.05$) difference between awake control measurements and those obtained after drug administration.

Abbreviations: PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

date, whereas most of the preocclusion blood pressures remained unchanged.

Arterial blood gas data are shown in Table 2. Oxygenation was similar in all groups and did not change significantly following drug administration. Thiopental was associated with an elevation of arterial partial pressure of carbon dioxide (PCO_2) at all time intervals. Diazepam and etomidate produced significantly increased arterial PCO_2 levels at 3 minutes. Ketamine resulted in significant increases in arterial PCO_2 3 and 10 minutes after drug administration.

Discussion

All of the drugs studied in this investigation have been used as induction agents for anesthesia. The doses utilized here were chosen because they maintain unconsciousness in dogs for the same amount of time as they do in human patients (24).

These drugs represent three pharmacologically distinct categories of central nervous system depressants: sedative hypnotics (thiopental, etomidate), a minor tranquilizer (diazepam), and a dissociative anesthetic (ketamine). The importance of knowing what these drugs do as individual entities lies in the fact that there are numerous clinical situations in which they are used as above, including monitoring patients during local or regional anesthesia, electroconvulsive therapy, and sedation for cardioversions and intubations, to name a few.

An important aspect of this investigation is the pharmacologic purity of the experimental model. Any effects seen had to be due only to these drugs because the preparation was not contaminated with other background anesthetics nor were the blood pressure manipulations done pharmacologically. Previous studies in this area (17,19,20,25) utilized vasoactive drugs to manipulate blood pressure or were associated with other anesthetic agents. When studying cardiovascular changes with blood pressure as a measured independent variable, blood pressure should not be changed by giving additional drugs such as nitroprusside or phenylephrine. This was why we opted to use a mechanical rather than a pharmacologic intervention. It is additionally noteworthy that our results apply to overall cardiovascular neuroregulatory function and cannot be attributed to an effect on any specific site such as arterial or atrial baroreceptors.

The alteration of the relation between heart rate and blood pressure by thiopental was profound. One prior study in chronically instrumented conscious animals, where the system was also pharmacologically pure, investigated the effects of pentobarbital on neuroregulation of the cardiovascular system (16). Although the method was different (that is, direct carotid sinus nerve stimulation), those results indicated that pentobarbital depressed important aspects of neurocirculatory control, particularly those related to the regulation of blood pressure and heart rate. Another barbiturate, methohexital, has also been studied in humans given nitrous oxide and morphine (26). In that setting, methohexital given by continuous infusion decreased the sensitivity of the arterial baroreflex arc. The extent of depression was found to be as potent as the depression seen from halothane and nitrous oxide. These previous studies, as well as our current data, confirm that barbiturates have a significant effect on circulatory reflexes.

Some data exist regarding benzodiazepines. Human studies in which morphine, diazepam, and nitrous oxide were combined have indicated that the depression of baroreceptor reflex control of heart rate is as significant as that seen with general anesthesia with isoflurane (17). That study did not, however, focus on diazepam alone. There are also data on the effects of diazepam and midazolam on circulatory reflexes in humans when blood pressure was altered pharmacologically with phenylephrine (19). In that study, both diazepam and midazolam decreased baroreflex sensitivity when given in doses of 0.4 and 0.3 mg/kg, respectively. The changes in baroreflex sensitivity with these two agents were quantitatively comparable, although it appeared that the depression lasted longer with midazolam than with diazepam. The data we obtained on diazepam in our conscious chronically instrumented animal model are similar to those of Marty et al. (19) in humans, with the exception that our blood pressure manipulations were mechanical and represented both pressor and depressor interventions rather than a pharmacologically induced increase in blood pressure.

The circulatory reflex effects of ketamine have not, to our knowledge, been specifically studied. Early on, there was controversy in the literature related to the mechanism of the cardiostimulatory effects of ketamine. One hypothesis was that of inhibition of afferent traffic from arterial baroreceptors (27). This was subsequently disproven, and it is now known that the cardiostimulatory effects of ketamine result from a central inhibition of parasympathetic outflow, as well as a catecholamine releasing effect (28). These actions apparently result in an impairment of the sensitivity of cardiopulmonary neurocirculatory reflexes. It may be that the overall stimulatory effect of ketamine has produced a set point for the circulatory system so high that minimal reactivity remains. This, of course, would apply only to the heart rate responses. We did not investigate vasoconstrictor or vasodilator responses resulting from circulatory reflexes. These may still be intact after ketamine. Further information is needed.

Etomidate has the least effect of all the drugs studied in terms of alteration in cardiopulmonary reflex control as modeled in this study. This is not surprising in view of the lack of generalized cardiovascular effects that are typically seen with administration of this drug.

It is worth considering whether, in this study, simultaneous alterations in heart rate, blood pressure, and arterial PCO_2 could have had an indirect impact on the results observed. The levels of hypercarbia we observed, although statistically elevated, were mild to moderate. All of the drugs elevated the arterial PCO_2 significantly 3 minutes after administration. With thiopental, diazepam, and ketamine, simultaneous depression of cardiovascular neural control was noted. With etomidate, this was not the case despite the fact that the PCO_2 was elevated. Thus, it is unlikely that PCO_2 changes had any noteworthy effect on the results. In addition, previous studies have shown that levels of PCO_2 higher than those we observed have no effect on the relation between RR interval and systolic pressure (9). The alterations in preocclusion heart rates probably also were not responsible for the effects observed. With thiopental and ketamine, the heart rate increased, but the reflex sensitivity was depressed. With diazepam, the sensitivity of the reflex was decreased even though the heart rate was unchanged, and with etomidate, the reflex sensitivity was not altered although the heart rate decreased. Thus, there does not seem to be any consistency in the relation between the sensitivity of these reflexes and the preocclusion heart rates. Furthermore, previous studies in conscious animals comparing normal animals with those in heart failure with elevated baseline heart rates have shown that heart rate does not affect the sensitivity of this reflex (29). This same logic applies to the blood pressure changes we observed. With thiopental and diazepam, the sensitivity of the reflex was depressed at 3 minutes, although the blood pressure was not altered from the conscious control. However, with ketamine, there was similar depression of the reflex, yet the blood pressure was elevated. Once again, previous studies support the idea that there may be enhancement of baroreceptor reflex function with lower systolic blood pressures as, for example, those that are noted during sleep (22). We are also sure that these results were not affected by interplay of peripheral and central chemoreceptors sensitive to hypoxia because all the animals were oxygenated prior to testing of the drugs. Thus, it is reasonable to attribute the changes in reflex sensitivity observed to the drugs themselves, rather than to indirect effects from simultaneous changes in blood gases and/or hemodynamics.

In this study, we deliberately used the term "neuroregulatory function" rather than "arterial baroreceptor function." The reflexes elicited with our mechanical methods are not purely arterial baroreceptor phenomena. Other baroreceptor functions in the circulatory system could also be simultaneously coming into play here; for example, low pressure baroreceptors on the right side of the circulation.

We also examined individual drugs specifically, rather than drug combinations. The benefit of knowing the pure effect of individual drugs, in addition to uses cited earlier, should help in making decisions for drug selection in various clinical situations. A drug that is depressant to neurocirculatory control reflexes may be a better choice than one that is stimulatory.

In conclusion, we examined the ability of four intravenous drugs commonly used as induction agents for anesthesia to alter the sensitivity of overall neurocirculatory control mechanisms. We utilized mechanical rather than pharmacologic methods for the manipulation of blood pressure in a conscious chronically instrumented animal to quantitate changes in heart rate. The results demonstrate considerable differences among the drugs studied.

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Epidural Morphine After Anterior Cruciate Ligament Repair: A Comparison with Patient-Controlled Intravenous Morphine

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LOPER KA, READY LB. Epidural morphine after anterior cruciate ligament repair: a comparison with patient-controlled intravenous morphine. Anesth Analg 1989;68:350–2.

To compare the management of postoperative pain using morphine administered by epidural catheter with intravenous patient-controlled analgesia (PCA), we prospectively studied 47 consecutive cases involving repair of the anterior cruciate ligament of the knee. Both the quality of analgesia and the incidence of side effects were documented. Compared with patients receiving PCA morphine, patients given epidural morphine reported significantly lower pain scores both at rest (0.7 ± 1.1 versus 3.4 ± 2.1, $P < 0.01$*) and with mobilization (3.2 ± 2.1 versus 6.1 ± 2.1,* $P < 0.01$*). Although patients receiving epidural morphine had a greater incidence of urinary retention, there were no significant differences in the incidence of nausea or pruritis. There was no respiratory depression in either group. We conclude that epidural morphine provides superior analgesia with a clinically inconsequential increase in side effects. Further, epidural morphine may have special advantages when early mobilization is indicated.*

Key words: ANESTHETIC TECHNIQUES—Epidural morphine. PAIN—Postoperative. ANALGESICS—morphine.

The management of postoperative pain is improved with the use of either epidural narcotics or intravenous patient-controlled analgesia (PCA). Neither technique is without an element of risk and an incidence of side effects. Whereas epidural morphine requires vigilance to detect occasional respiratory depression (1), intravenous PCA requires expensive machines subject to mechanical failure or human errors (2). Narcotics, regardless of the route of administration, involve bothersome side effects including pruritus, nausea, and urinary retention. Few studies have compared the management of postoperative pain with epidural morphine to PCA, focusing on analgesic scores or post-Cesarean section patients (3–6). The purpose of this report is to evaluate both the quality of analgesia and the incidence of side effects resulting from the management of postoperative pain with either epidural morphine or intravenous morphine with PCA after a painful orthopedic procedure.

Methods

With the approval of our institutional human investigation committee, a prospective, nonrandomized study was undertaken of 47 consecutive patients in whom postoperative pain after repair of the anterior cruciate ligament (ACL) of the knee was managed by our anesthesiology-based acute pain service (APS). The surgery was performed by the same orthopedist. All pertinent information during the course of treatment was collected on specially designed patient care sheets, checked for completeness, entered in a computer database, then retrieved and evaluated at a later time for this investigation. All patients were healthy, ASA physical status I, individuals ranging from age 15 to 39 years.

For their operative procedure, patients were offered either an epidural or a general anesthetic. The patients understood that an epidural anesthetic would be followed by epidural analgesia, whereas a general anesthetic would be followed by intravenous PCA.

General anesthesia, when chosen, was induced with thiopental, 4–6 mg/kg, and maintained with O_2:N_2O, 40:60, and 1.0–1.5 MAC isoflurane. Narcotic administration was begun in the recovery room. Once the patient was comfortable, PCA with intravenous morphine was instituted. The incremental dose

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of morphine was 1 mg, the lockout interval was set at 8 minutes, and the 4 hour maximum dose of morphine allowed was 30 mg. If pain persisted, the incremental dose of morphine was increased to 1.5 mg and/or the lockout period decreased to 6 minutes.

Epidural anesthesia, when chosen, was established by injecting lidocaine 2% or bupivacaine 0.5% into a catheter placed at either the L2-3 or L3-4 interspace. Sedation was provided at the discretion of the anesthesiologist. Epidural opiate was limited to preservative-free morphine (an undiluted 0.1% solution of Duramorph, A. H. Robins). The initial 4-mg dose of morphine was administered in the operating room by the attending anesthesiologist approximately 1 hour before the expected completion of surgery. In the recovery room, the APS assumed responsibility for ensuring the adequacy of analgesia when the local anesthetic block receded. Subsequent morphine doses and intervals between epidural injections were adjusted as needed for each patient to establish maximum comfort at rest and to permit movement and ambulation without severe pain. Treatment with either epidural or intravenous PCA morphine was continued until a fluid diet was prescribed by the surgeon at which time incisional pain could be effectively controlled by an oral analgesic.

The following information was collected by the APS on daily rounds: 1) the effective 24-hour morphine dose with each technique; 2) self-assessment by patients of the incisional pain both at rest and with ambulation with use of a 0 to 10 verbal analogue scale (0 = "no pain," 10 = "the most severe pain imaginable"); 3) the incidence and severity of side effects including pruritus and nausea (0 = none; 1 = mild, no medications requested; 2 = moderate, medications requested and effective; 3 = severe, medications administered but not effective); 4) the incidence and severity of urinary retention (0 = none; 1 = hesitancy; 2 = one or two bladder catheterizations needed; 3 = >2 bladder catheterizations or a Foley catheter required); 5) the incidence of respiratory depression (respiratory rate <8) as detected by a nurse at hourly checks.

Statistical analysis of parametric data was performed with use of the chi-square test. The Mann-Whitney test was used for nonparametric data. Statistical significance was assigned at $P < 0.05$.

Results

Of 47 consecutive cases studied, postoperative pain was managed with epidural morphine in 30 patients and with intravenous PCA morphine in 17 patients. Although there were no significant differences in the demographic data of these two groups, patients managed with an epidural catheter required a significantly lower 24-hour morphine dosage (Table 1).

Table 1. Patient Characteristics and Management

Parameter	Epidural	PCA
N	30	17
Sex (m:f)	14:16	11:6
Age (yr)	25 ± 6 (18–39)	24 ± 7 (15–36)
Morphine dosage over first 24 hours (mg)	12 ± 6 (4–32)	64 ± 24 (32–101)*

*$P < 0.05$. Values expressed as means ± SD.

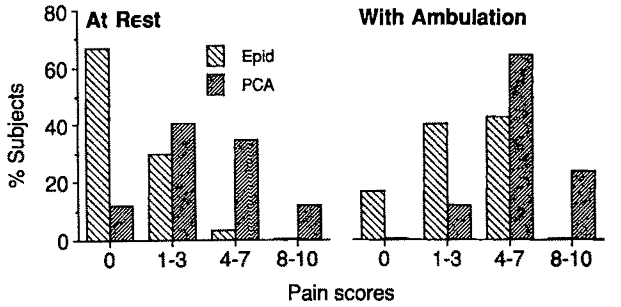

Figure 1. Distribution of pain scores. The pain scores were self-assessed by the patient with the use of a 0 to 10 verbal analogue scale, 0 = "no pain" and 10 = "the most severe pain imaginable."

Patients managed with epidural morphine reported significantly lower pain scores both at rest and with ambulation than those of PCA patients (0.7 ± 1.1 versus 3.4 ± 2.1, $P < 0.01$, and 3.2 ± 2.1 versus 6.1 ± 2.1, $P < 0.01$, respectively). Figure 1 shows the distribution of pain scores both at rest and with ambulation on the first postoperative day. Though patients receiving epidural morphine had a significantly higher incidence of moderate urinary retention, there were no significant differences with respect to the incidence of pruritus or nausea (Table 2). There was no respiratory depression in either group at any point in the study.

Discussion

Among the reports attesting to the advantages of managing postoperative pain with either epidural or intravenous PCA narcotics, there is little information comparing these methods with respect to both the analgesic quality achieved and the incidence of side effects. The only previous report comparing epidural narcotics to PCA, with respect to both analgesia and side effects, found PCA to be an excellent alternative to epidural morphine (6). However, that study was limited to a single dose of epidural morphine.

Table 2. Incidence of Side Effects

	Zero	Mild	Moderate	Severe
PCA ($N = 17$)				
Pruritus	11 (65%)	3 (18%)	1 (6%)	2 (11%)
Nausea	8 (47%)	7 (41%)	2 (12%)	0 (0%)
Urinary Retention	13 (76%)	1 (6%)	1 (6%)	2 (12%)
Epidural ($N = 30$)				
Pruritus	8 (27%)	12 (40%)	7 (23%)	3 (3%)
Nausea	9 (30%)	7 (23%)	7 (23%)	7 (23%)
Urinary Retention	14 (47%)	0 (0%)	13 (43%)*	3 (10%)

*$P < 0.05$.

Patients presenting for repair of the anterior cruciate ligament of the knee represent a healthy surgical population undergoing a single procedure expected to cause severe pain. The relatively young age of these patients tends to eliminate previously described pain modifiers, such as old age, chronic pain, and learned helplessness (7).

The responsibility for postoperative pain management after all major surgery at our institution has been assumed by an anesthesiology-based team. This allows for continuity of pain control from the operating room through recovery on the ward. Therefore, with consideration for patient preferences, a comprehensive plan for both anesthesia and analgesia may be adopted. Optimal titration of morphine by either technique was ensured by frequent evaluation. In consultation with the APS, nurses can vary the dosage of the epidural morphine or change the parameters of the intravenous PCA pump as necessary to maximize patient comfort.

Early joint mobilization after certain orthopedic procedures is currently favored by orthopedists but may be limited by severe pain. Previous studies (3–6) failed to distinguish between pain at rest and with movement. We found that epidural morphine provided more profound analgesia under both circumstances.

It should be noted that this is a nonrandomized study. The two groups of patients received different anesthetic techniques. In the present study, one can not be certain whether those patients who chose an epidural anesthetic or an inhalational anesthesic would have different responses to pain.

The observation that patients receiving morphine by an intravenous PCA system did not attain profound analgesia is in agreement with other studies (7,8). This may reflect the limitation imposed by increased side effects with the greater doses of intravenous narcotics needed for severe pain.

The low incidence of side effects associated with epidural morphine in this study may reflect our strategy of frequent low-dose administration of morphine (typically 4 mg at 6–8 hour intervals). The higher incidence of moderate urinary retention did not cause major clinical concern given the greater analgesic relief provided by epidural morphine.

In summary, we have shown that after a single surgical procedure involving the lower extremity, epidural morphine provides greater patient comfort both at rest and with ambulation than does intravenous morphine with PCA. Further, the superior quality of analgesia provided by epidural morphine is not associated with a clinically significant increase in side effects. If greater patient comfort permits earlier mobilization, a more rapid recovery may ensue.

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Epidural Analgesia With Bupivacaine Reduces Postoperative Paralytic Ileus After Hysterectomy

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WATTWIL M, THORÉN T, HENNERDAL S, GARVILL J-E. Epidural analgesic with bupivacaine reduces postoperative paralytic ileus after hysterectomy. Anesth Analg 1989;68:353–8.

This study was undertaken to compare the effects of postoperative bupivacaine epidural analgesia with those of intermittent injections of ketobemidone (a synthetic opioid) on postoperative bowel motility in patients who had had hysterectomies. The epidural group (N = 20) received continuous epidural anesthesia with bupivacaine postoperatively for 26–30 hours and the control group (N = 20) received intermittent injections of ketobemidone for postoperative pain relief. Postoperative bowel movements and propulsive colonic motility were estimated from the first passage of flatus and feces and by following radiopaque markers by serial abdominal radiographs. In the epidural group, the times for first passing of flatus (31 ± 22 hours; mean ± SD) and feces (70 ± 44 hours) were significantly shorter than in the control group (flatus 58 ± 14 hours and feces 103 ± 26 hours). The average position of the markers was significantly more distally in the epidural group immediately after operation and the markers continued to move forward during the first postoperative day. In the control group, the markers did not move during this period. The results demonstrate that postoperative bowel peristalsis returned earlier in the patients given epidural analgesia with bupivacaine for pain relief than in patients given a narcotic.

Key Words: ANALGESICS—opioids. ANESTHETICS LOCAL—bupivacaine. ANESTHETIC TECHNIQUES—epidural. GASTROINTESTINAL MOTILITY—colon. PAIN—postoperative. SURGERY, ABDOMINAL—hysterectomy

Abdominal surgery inhibits gastrointestinal motility. This inhibition, "postoperative ileus," is most marked and persistent in the colon (1) and is considered to be due to activation of spinal reflexes originating from the abdominal cavity with the sympathetic nerves as the efferent nerves. As a means of blocking these reflexes while producing pain relief, epidural analgesia (EDA) has been proposed and used postoperatively (2,3), but the results in terms of return of bowel movements are ambiguous (3,4). Postoperative pain relief is commonly achieved by use of parenteral opioids. However, parenteral opioids diminish propulsive gastrointestinal motility (3,5), as also do epidural opioids (3,6).

The present study was undertaken to compare the effects of continuous bupivacaine postoperative epidural analgesia with those of intermittent intramuscular injections of ketobemidone (a synthetic opioid) on postoperative bowel motility in patients who had undergone hysterectomy. As opioids inhibit intestinal motility, these were excluded both pre- and perioperatively in the epidural group. Bowel motility was assessed both from passage of flatus and feces and by the use of radiopaque markers (4).

Methods and Material

The study was approved by the Ethics Committee of Örebro County Council and informed consent was obtained from all patients. Forty patients (ASA physical status I and II) scheduled for hysterectomy were studied (Table 1). Most patients were operated on for myoma, but four patients in each group (see next paragraph) had carcinoma. The patients had a history of normal bowel habits. No patient was taking any drugs known to influence gastrointestinal motility. On the night before surgery, all patients received an

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Table 1. Data for the Patients in the Epidural Analgesia (EDA) Group and the Control Group

	EDA Group	Control Group
No.	20	20
Age (yr)	50 ± 10	49 ± 11
Weight (kg)	69 ± 15	67 ± 11
Height (cm)	164 ± 6	165 ± 5

enema. All patients were premedicated with dixyrazin 0.6–0.7 mg/kg of body weight.

Before operation, the patients were randomly allocated to two groups. One group (the EDA group) received epidural anesthesia in combination with light general anesthesia intra-operatively and continuous bupivacaine epidural analgesia postoperatively for 26–30 hours. The other group (control group) received general anesthesia intra-operatively and intermittent intramuscular injections of 5 mg ketobemidone (an opioid agent equipotent with morphine) for postoperative pain relief. In the EDA group, the epidural catheter was inserted at the T12-L1 level before induction of general anesthesia and an amount of 0.5% bupivacaine adequate to achieve sensory block (pin-prick) to at least the T6 level was given. In both groups, general anesthesia was induced with thiopental and maintained with 70% nitrous oxide in oxygen and isoflurane. Intra-operative fentanyl was given in the control group, but no opioids were administered in the EDA group. Muscle relaxation was achieved and maintained with pancuronium bromide in both groups. At the end of operation, residual muscle relaxation was antagonized with neostigmine preceded by atropine.

Bowel movements and propulsive colonic motility

The first passage of flatus and/or feces was recorded by the ward nurses. Propulsive colonic motility was studied by the use of radiopaque markers (4,7). On the night before surgery, the patients swallowed four radiopaque markers of different shapes. The markers (0.10–0.20 g) consisted of 10–20 mm of a hollow radiopaque polyethylene tube. Two of the four were filled with barium sulfate powder and sealed at the ends.

The transit of the markers was followed by means of plain abdominal radiographs taken immediately after the operation (R_0) and then every 12 hours (R_1-R_7), starting in the morning on the first postoperative day and continuing until one of the markers reached the sigmoid-rectum or until the fourth postoperative day. For ethical reasons no patient had more than eight radiographs. The colon was divided into four segments: Segment 0 (cecum and ascending colon), segment 1 (transverse colon), segment 2 (descending colon), and segment 3 (sigmoid-rectum). The average position of the markers was calculated for every radiographic examination time.

Postoperative pain relief

A continuous infusion of 0.25% bupivacaine at 8 ml/hour was started immediately after the operation in the EDA group and was maintained until 4 PM on the first postoperative day. If the level of sensory block was lower than T6 or if the patient complained of pain, additional doses of 0.5% bupivacaine were administered. If patients in this group still complained of pain, ketobemidone was given.

In the control group, postoperative pain relief was achieved by intermittent injections of 5 mg ketobemidone given when requested. In the afternoon of the first postoperative day before ending EDA (26–30 hours postoperatively) or at the corresponding time in the control group, the level of pain at that moment was estimated with the use of a visual analog scale (VAS 0-10: 0 = no pain, 10 = as bad as pain can be). Pain scores on a 5 point scale (no pain = 0, slight pain = 1, moderate pain = 2, severe pain = 3 and unbearable pain = 4) were also used to estimate the pain experienced during the whole of the first 24 hour period.

Blood glucose concentrations

Venous blood samples for measurement of blood glucose concentrations were obtained immediately before anesthesia, before skin incision, and 1, 3, 6, 9, and 20 hours after skin incision. Blood glucose concentrations were measured by a glucose oxidase method. Only acetated Ringer's solution was given intravenously during the period of blood glucose assessments. The duration of the operation was recorded and intra-operative bleeding was clinically estimated. Postoperatively any nausea or vomiting was recorded and the length of time before discharge from the hospital was compared between the two groups.

Statistics

Results are presented as mean ± SD. All differences were tested for statistical significance by means of the

Table 2. Postoperative Bowel Movements

	EDA Group	Control Group	Significance
Time (hr) before passing flatus			
Mean ± SD	31 ± 22	58 ± 14	$P < 0.002$
Range	(0.5–78)	(33–96)	
Time (hr) before passing feces			
Mean ± SD	70 ± 44	103 ± 26	$P < 0.02$
Range	(0.5–140)	(49–144)	

Mann-Whitney U test with the exception of blood glucose concentrations, for which Student's *t* test was used. A P value of less than 0.05 was considered statistically significant.

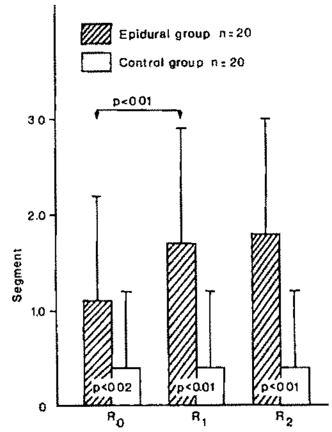

Figure 1. Position of the radiopaque markers immediately postoperatively (R_0) and in the morning (R_1) and in the evening (R_2) on the first postoperative day. Propulsive colonic motility was greater in the epidural group both during surgery and postoperatively.

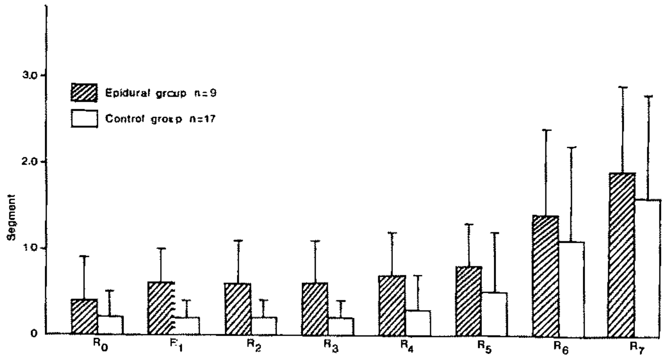

Figure 2. Position of the radiopaque markers after exclusion of patients where at least one marker had reached the sigmoido-rectal segment of colon during the first postoperative day. The differences between the remaining patients in the two groups are not statistically significant.

Results

Patient characteristics in the two groups were comparable (Table 1). There were no differences in operation time (EDA group 101 ± 31 minutes, control group 98 ± 31 minutes) or intra-operative bleeding (EDA group 340 ± 190 ml, control group 339 ± 196 ml).

Bowel movements

The times that elapsed before the first passage of flatus and feces were significantly shorter in the EDA group (Table 2) and four patients in this group defecated within 30 minutes after surgery.

The radiographs taken immediately after the operation (R_0) showed that the markers in the epidural group were located significantly more distally than in the control group (Fig. 1). On the first day postoperatively (R_1 and R_2) the markers continued to move forward in the patients having epidural analgesia, but the position of the markers in the control patients remained unchanged (Fig. 1). In the evening of the first postoperative day the radiographs (R_2) showed that at least one marker had reached segment 3 (sigmoid-rectum) in 11 patients in the EDA group and in 3 patients in the control group. Therefore, no more radiographs were taken in these patients. Even when these patients were excluded, the starting position of the markers in the remaining EDA patients ($N = 9$) was more distal but not significantly so than in the remaining control patients ($N = 17$). In these EDA patients, during the period of epidural analgesia (R_1 and R_2), the markers moved slowly forward, but when the epidural analgesia was ended, the forward transportation diminished but increased again at R_6 and R_7 (Fig. 2). In the remaining patients in the control group after the exclusions, the markers did not move until R_4, and the forward transportation increased at R_6 and R_7 (Fig. 2).

Retrograde movements of the markers occurred on some occasion in 10 patients in the EDA group and in 5 patients in the control group.

Postoperatively on the day of operation no patient in the EDA group but six patients in the control group complained of nausea. Three of these 6 patients vomited and two of them had severe pain during

Table 3. Postoperative Pain Relief

	EDA Group	Control Group	Significance
VAS (score)	1.9 ± 1.4	4.4 ± 2.5	$P < 0.01$
Pain scores (0–4)	0.6 ± 0.7	1.3 ± 0.9	$P < 0.01$

VAS (0 = no pain, 10 = pain as bad as pain can be) before termination of epidural analgesia (26–30 hr postoperatively) and at the corresponding time in the control group. Pain scores (0 = no pain, 4 = unbearable pain) as an estimation of the pain during the first 24 postoperative hours.

vomiting. On the first postoperative day, three patients, all in the control group, experienced nausea.

The patients in the EDA group began to drink after 38 ± 26 hours and to eat after 70 ± 26 hours, compared with 47 ± 20 and 77 ± 19 hours, respectively, in the control group. These differences were not statistically significant.

Postoperative pain relief

Before EDA was terminated on the first postoperative day, pain relief as estimated by VAS was significantly better in the EDA group (Table 3). The pain scores for the postoperative period before discontinuation of EDA or at the corresponding time in the control group were also better in the EDA group (Table 3). During the day of operation, the patients were given ketobemidone (5 mg) on an average of 0.15 ± 0.4 occasions in the EDA group and on 4.0 ± 1.5 occasions in the control group. The corresponding numbers of occasions during the first postoperative day were 2.5 ± 1.5 and 4.1 ± 1.2, respectively. However, epidural analgesia was terminated at 4 PM on the first postoperative day and most of the ketobemidone was given after that time in the EDA group. After the day of operation, ketobemidone was given for 1.8 ± 1.0 days in the EDA group and for 2.1 ± 0.8 days in the control group. Thereafter, tablets (acetaminophen 500 mg, codeine 30 mg) were given for pain relief and analgesics were required for 3.8 ± 2.8 days in the EDA group and for 3.4 ± 2.6 days in the control group after the day of operation.

Blood glucose

The blood glucose concentrations were significantly lower in the EDA group 3, 6 and 9 hours after skin incision. In the morning on the first postoperative day there were no differences between the groups (Fig. 3).

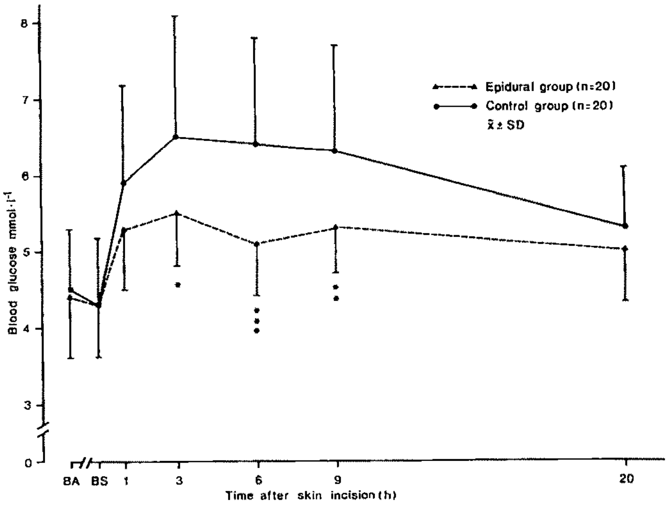

Figure 3. Blood glucose concentration (mmol × 1^{-1}) before anesthesia (BA), before surgery (BS) and 1, 3, 6, 9, and 20 hours after skin incision. The blood glucose concentrations were significantly lower in the epidural group, 3, 6, and 9 hours after skin incision. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Length of hospital stay

The differences in the length of hospital stay between the EDA and control groups (7.7 ± 1.2 and 7.4 ± 1.5 days, respectively) was not significant.

Discussion

In this study, bowel movements returned earlier in the group of patients given epidural analgesia with bupivacaine for postoperative pain relief than in the patients given intramuscular opioids (ketobemidone). Parenteral opioids are known to delay gastrointestinal transit (5) and therefore opioids were avoided both pre- and intra-operatively in the epidural group. Postoperatively, opioids were given only on very rare occasions in the EDA group and were not always given for abdominal pain but rather for pain at other sites. As in a similar study (4), epidural analgesia reduced the hyperglycemic response to surgery. This confirmed that blockade of the sympathetic efferents to the abdominal cavity had been achieved.

Different methods have been used to study bowel movements postoperatively (1–4,7–9). Clinically, passage of flatus and feces seems to be a reliable sign of the return of intestinal movements (3,10). However, it has been postulated that "a more conclusive method to study propulsive motility in the colon is the use of radiopaque markers and serial abdominal radiographs" (4). Both the first passage of flatus and feces and the position of the radiopaque markers showed earlier bowel movements in the epidural group. However, the positions of the markers immediately postoperatively differed from those observed in other studies with similar markers (4,7). In the epidural group, the markers were located significantly more distally in the colon, which meant that there was propulsive colonic motility during the operation in the patients who underwent surgery under epidural anesthesia. Even during the immediate postoperative period when epidural analgesia was used for pain relief, the markers continued to move forward in the epidural group, while the position of the markers at a corresponding time was unchanged in the control group. At 4 PM on the first postoperative day, the epidural analgesia was terminated and subsequently all patients received intramuscular opioids for pain relief on request. In those patient in whom the radiologic examination continued (as no marker had reached segment 3), there were no differences between the epidural and the control group concerning propulsive movements of the markers. In several patients in both groups, retrograde movements of the markers occurred. Retrograde movements are normally frequent in the ascending colon but are infrequent in the transverse colon and descending colon (11). Evaluation of the propulsive colonic motility from the radiographs may have been disturbed by these retrograde movements and also by the fact that in some patients the first passage of flatus and feces occurred while the markers were still in the ascending colon.

Epidural opioids, like parenteral opioids, also delay gastrointestinal motility (3,6,12), whereas thoracic epidural anesthesia with block of the efferent innervation of the stomach and small intestine does not increase gastric emptying or gastrointestinal propulsive motility; but it does not delay gastric emptying or depress intestinal motility to the extent epidural morphine does (6). It has also been shown that a combination of epidural bupivacaine and epidural morphine does not shorten the duration of postoperative ileus (13). It may therefore be concluded that when epidural analgesia with local anesthetics is replaced by or combined with opioids, the negative effects of the latter on gastrointestinal motility become evident. Besides the negative effect of ketobemidone on intestinal motility, the incidence of nausea and vomiting was also more frequent in the control group. The patients in the EDA group began to drink earlier, but neither in this respect nor in terms of the length of time before intake of food did EDA patients differ significantly from the control group.

There were no differences in the duration of operation or the amount of bleeding between the two groups. Despite good pain relief and earlier bowel movements in the EDA group, this did not result in earlier discharge from hospital in these patients. The length of hospital stay was about 7.5 days in both groups.

The epidural analgesia was effective, as judged from the pain scores and the hyperglycemic response to surgery, and bowel movements returned more rapidly (though still were not normal). It has been shown that gastric emptying is delayed intraoperatively during relatively short orthopedic operations on the lower extremities during spinal anesthesia despite good pain relief (14), and it has therefore been suggested that factors other than pain may influence gastrointestinal motility during and after surgery. Rennie et al. (15) in a study of neural and humoral factors affecting postoperative ileus found that dopamine, a possible peripheral neurotransmitter, reduced the activity of isolated colonic smooth muscle and that the plasma motilin level, suppressed intra-operatively, increased postoperatively with the return of normal bowel motility.

In conclusion, postoperative bowel movements returned earlier in patients who were given epidural analgesia with bupivacaine postoperatively for pain relief than in patients given ketobemidone, an opioid. To shorten the postoperative duration of ileus, the use of epidural analgesia with local anesthetics for pain relief is a suitable method, and opioids should be avoided as long as possible.

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Aging: Effects on Minimum Alveolar Concentration (MAC) for Halothane in Fischer-344 Rats

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It is well-established that the anesthetic requirement (MAC) of volatile agents such as halothane is reduced in elderly patients. The current project was designed to determine whether a similar alteration in anesthetic requirement occurs in Fischer-344 (F-344) rats, an animal model often utilized in physiology and pharmacology to examine aging-related changes. Animals were exposed to increasing or decreasing levels of halothane. After equilibration at each concentration, the response to tail-clamping was used for MAC testing. MAC was reduced approximately 17% in aged (25 months) versus young adult (5 months) animals. From these data, it is concluded that the F-344 rat may be an adequate model for examination of age-dependent alterations in the actions of volatile anesthetics.

Key Words: ANESTHETICS, VOLATILE: halothane. POTENCY, ANESTHETIC: MAC. AGE FACTORS: MAC.

The number of geriatric patients in the United States requiring surgical procedures is expected to grow rapidly between 1986 and the year 2020 (1). During this period, the population aged 65 years and older is expected to increase approximately 2% annually, resulting in an average addition of 750,000 elderly individuals each year (1). Furthermore, the number of persons aged 85 years and older is projected to increase at an even faster pace, approximately 3% per year (1). With advanced age, there is an increased incidence of diseases requiring surgical intervention and therefore anesthesia. Consequently, it is expected that more than half of the persons above 65 years of age will undergo surgery during the remainder of their life (2,3). This projected increase of surgical procedures in the elderly mandates a better understanding of aging-related alterations in responsiveness to anesthetics and the mechanisms underlying these changes.

It is well-known that minimum alveolar concentration (MAC) for volatile anesthetics is decreased in the elderly (4–6). Investigations of the mechanism(s) underlying age-dependent alterations in MAC would greatly benefit from an appropriate animal model. Rats have been used frequently to study anesthetic potency including changes in MAC induced by hypo- or hyperthyroidism (7), body temperature (8,9), circadian rhythm (10), and pregnancy (11). Studies of aging-associated changes in responsiveness to a number of drugs have commonly used the Fischer-344 (F-344) rat as a model. However, age-related alterations in the anesthetic potency of halothane have not been defined for this rat strain. Therefore, the present study was designed to determine MAC values for halothane in 5 month-old (young adult), 14 month-old (adult) and 25 month-old (aged or senescent) F-344 rats.

Methods

Animals

Male F-344 rats (5, 14, and 25 months of age with mean weights of 325, 440, and 410 g, respectively)

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were purchased from Harlan Sprague-Dawley, Inc. (Indianapolis, IN) and maintained for at least 7 days in the Division of Animal Laboratory Medicine with free access to food and water. These animals were raised here under a contract with the National Institute on Aging. All procedures in this study were approved by our Animal Research Care Committee.

MAC Determination

Spontaneously breathing rats were exposed to halothane in a 25-cm long clear, cylindrical chamber with a 7-cm inner diameter that did not allow the animals to turn around (12). The anesthetic mixture (halothane in 100% O_2) was delivered by an anesthesia machine (Foregger, Smithtown, NY) with a calibrated vaporizer (Fluomatic, OH, Madison, WI) at a flow rate of 2.5 liters/minute. Concentrations of halothane entering and exiting the chamber were monitored by an anesthetic agent analyzer (Model AAM 222, Puritan-Bennett, Wilmington, MA). The analyzer was calibrated daily with a 2.005 vol% halothane/O_2 mixture (Scott Medical Products, Plumsteadville, PA). The anesthetic concentration exiting the chamber reached equilibrium with that entering within 5-6 minutes and remained constant thereafter. Rectal temperature was monitored and maintained within ±0.4°C of pre-anesthetic values with a heating lamp controlled thermostatically by a rectal thermistor probe (Yellow Springs Instruments, Yellow Springs, OH). In each experiment, blood was drawn from a tail vein before and at the end of exposure to the anesthetic. P_{0_2}, P_{CO_2} and pH were measured with use of a Radiometer blood-gas analyzer (Model ABL2 Acid-Base Laboratory, Radiometer America Inc., Orlando, FL).

MAC was determined in 5 month-old (N = 13), 14 month-old (N = 13), and 25 month-old (N = 12) F-344 rats with the use of a method similar to that described by White et al. (13). To minimize variations in anesthetic requirement due to circadian rhythm (10), all experiments were begun at the same time of day (8:30 AM). Animals were exposed to a constant anesthetic concentration for 2.5 hours before applying test stimuli. The 2.5 hours exposure time was chosen 1) to achieve F_I/F_A ratios reasonably close to 1.0 (13), and 2) to keep the total anesthetic exposure time at 10 hours or less. A rubber-clad vascular clamp (22 cm DeBakey) was clamped for 45 seconds across the proximal third of the tail. Purposeful movement of either hind limb and/or the head was noted as a positive response. Depending on the reaction, the anesthetic concentration was increased or decreased by 0.08–0.10 vol%, and the reaction to clamping was tested again after 2.5 hours exposure to the new constant level. This procedure was repeated until both a positive and a negative response were obtained. No animal required exposure to more than four anesthetic concentrations. In each animal, MAC was determined as the mean of the highest inspired anesthetic concentration at which a positive response occurred and the lowest concentration at which no response was observed.

Table 1. Effect of Age on MAC for Halothane in F-344 Rats

Age (mo)	*N*	MAC (vol%)
5	13	1.23 ± 0.03*
14	13	1.21 ± 0.02*
25	12	1.05 ± 0.02

*Significantly different from values in 25 month-old rats.

Statistical Analysis

Data were evaluated with the use of analysis of variance, and values were compared by Duncan's multiple range test. Criterion for statistical significance was a P value less than 0.05. All data are presented as means ± SEM.

Results

As shown in Table 1, MAC in 25 month-old rats was significantly lower (15 to 17%) than that in 5 or 14 month-old animals. There was, however, no significant difference between MAC values obtained in 5 and 14 month-old rats.

To determine whether alterations in acid-base balance were involved in the aging-associated change in MAC, P_{O_2}, P_{CO_2} and pH were measured before and at the end of the exposure to halothane (Table 2). Rats were breathing spontaneously. Their respiratory patterns did not change noticeably, and they displayed no signs of respiratory distress (13) during the course of the experiment. Mean venous P_{O_2} values at the end of the experiment were greater than 140 mm Hg in all age groups, indicating that adequate oxygenation was maintained. Blood gas tensions obtained before exposure to halothane showed no age-related differences. In 5 month-old animals, P_{CO_2} and pH were not affected by continuous exposure to halothane. A reduction in pH and an elevation in P_{CO_2} did occur in both 14 and 25 month-old rats. There were, however, no statistically significant differences between values

Table 2. Effect of Age on Venous pH and P_{CO_2} in F-344 Rats Before and After Prolonged Exposure to Halothane

Age (mo)	pH		P_{CO_3} (mm Hg)	
	before	after	before	after
5	7.41 ± 0.02	7.39 ± 0.01	41.7 ± 2.4	43.9 ± 1.8
14	7.42 ± 0.01	7.34 ± 0.02*	41.6 ± 1.8	57.2 ± 1.7*
25	7.43 ± 0.02	7.33 ± 0.03*	44.0 ± 2.0	60.6 ± 3.8*

*Significantly different from corresponding value in 5 month-old rats.

in these two age groups. Because the average duration of anesthesia in the various age groups did not vary significantly (7.1 ± 0.6, 6.1 ± 0.5, and 6.5 ± 0.5 hours in 5, 14, and 25 month-old rats, respectively), the data suggest that 14 and 25 month-old animals were more susceptible than the 5 month-old animals to the development of respiratory acidosis associated with prolonged exposure to halothane.

The mean pre-anesthetic rectal temperature in aged rats was lower than in 5 and 14 month-old rats (37.4 ± 0.2°C versus 38.2 ± 0.1°C and 38.1 ± 0.1°C, respectively). Because animals were maintained under a thermostatically controlled heating lamp throughout the experiments, no significant temperature changes were observed in any age group.

Discussion

The present results suggest that age-dependent reductions in anesthetic requirement for halothane begin only after adulthood (14 months of age) has been achieved in F-344 rats. In contrast, studies in humans have shown a progressive age-related decline in anesthetic requirement beginning after puberty (4–6,14). Similarly, other investigators reported a difference in MAC for halothane in young adult and adult Sprague-Dawley (SD) rats (13). It seems, therefore, that the delayed onset of age-related decline of MAC in F-344 rats may be unique to this strain.

Merkel and Eger et al. (15,16) used alveolar anesthetic concentration (measured as end-tidal concentration) as the index most closely related to brain anesthetic tension. Under truly steady-state conditions, end-tidal concentration of an anesthetic equals not only its alveolar concentration (F_A) but also its inspired concentration (F_I). The present determination of MAC utilized measurements of F_I after a 2.5 hour equilibration time. Anesthetic F_I/F_A ratios ranging from 0.9–1.3 have been reported for young adult and adult SD rats after a 2.5 hour exposure to halothane (13). Thus, it is possible that the use of F_I in the present study overestimated MAC by approximately 10% in both 5 and 14 month-old animals. The time course for halothane equilibration has not been determined for aged rats. However, age-related changes in regional blood flow (17) and in the solubility of halothane in tissues (18–20) suggest an increase in the F_I/F_A ratio during senescence and, thus even a greater overestimation of MAC in aged animals. Comparison of data obtained after 2.5 hours with those obtained after prolonged exposure to halothane (maximally 10 hours) should not introduce a bias in this study; it has been shown that determination of MAC is not affected by the duration of anesthetic exposure (12,16).

To insure that the enhanced responsiveness to halothane-induced anesthesia in aged rats was a result of senescence and not other factors, factors known to influence MAC (e.g., temperature, P_{O_2} and P_{CO_2}) were monitored. During prolonged exposure to near MAC concentrations of halothane, venous pH decreased and P_{CO_2} increased in 14 and 25 month-old rats, whereas no significant changes in these parameters occurred in young adults. However, neither the reduction in pH (0.1 pH-units average) nor the elevation in P_{CO_2} observed in the present study were sufficient to affect anesthetic requirement. It has been reported that MAC is reduced only when arterial P_{CO_2} levels rise above 95 mm Hg (21). Venous P_{CO_2} never exceeded 61 mm Hg in the current study. Furthermore, the fact that similar changes in pH and P_{CO_2} occurred in both 14 and 25 month-old rats, whereas MAC was reduced only in 25 month-old animals, supports the notion that the determination of MAC was not significantly influenced by changes in pH and P_{CO_2}. Venous P_{O_2} remained at levels above 140 mm Hg throughout the experiments. Because it is unlikely that the arterial P_{O_2} was lower than the venous one, it would appear that alterations in P_{O_2} did not influence the determination of MAC in the present study.

Rectal temperatures of the rats did not change during MAC determination in the current study. However, as reported by other investigators (22,23), initial mean body temperature was lower in aged rats than in either 5 or 14 month-old animals. Because changes in body temperature influence MAC in humans (24), in dogs (25), and in rats (8,9), it is possible that the lower body temperature of aged rats contributed to the decline in anesthetic requirement. However, a 1°C decrease in body temperature resulted in a 4.8 (8) to 6.2% (9) reduction of halothane MAC in SD rats. It is, therefore, unlikely that the 17% decrease in MAC observed in the current study was caused solely by the 0.8°C difference in body temperature observed in 4 and 25 month-old F-344 rats.

MAC values for halothane in F-344 rats determined in the current study compare favorably with those reported for SD rats (9,13). Furthermore, the age-dependent reduction in MAC observed in our F-344 rats was similar to that described in elderly humans (4,14); although the magnitude of decline from adulthood to senescence was smaller, and the onset of the change in MAC seemed to occur later in life in rats. Thus, the present data imply that the F-344 rat may be used as a model for studying mechanisms underlying aging-related changes in the effects of volatile anesthetics, provided that the previously mentioned differences are taken into account.

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Influence of Dornier HM3 System on Respiration During Extracorporeal Shock-Wave Lithotripsy

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BROMAGE PR, BONSU AK, EL-FAQIH, SR. Influence of dornier HM3 system on respiration during extracorporeal shock-wave lithotripsy. Anesth Analg 1989;68:363-7.

Patients undergoing extracorporeal shock-wave lithotripsy (ESWL) for renal stones in the Dornier HM3 apparatus are immersed to the clavicles in water and anchored by abdominal and leg restraining straps. The respiratory effects of this system and sedation with midazolam were studied in 70 awake patients anesthetized with epidural blockade. On immersion, surface abdominal pressure and respiratory frequency (f) increased. Tidal volume (VT) and arterial saturation (SaO_2) decreased. After intravenous midazolam 0.045 mg/kg body weight, VT decreased further to 35% below pre-immersion values and stone excursions measured by fluoroscopy diminished by more than 50%; reduction of VT and stone excursions were linearly correlated (R = 0.45). SaO_2 declined sharply to 6.1% (range −1.5–−13.8%) below pre-immersion values, whereas end-tidal CO_2 ($PETCO_2$) increased more slowly and f remained above the pre-immersion rate. In three patients, SaO_2 decreased to below 85% but was rapidly restored to 98–100% by oxygen administration. The respiratory effects of sedative drugs are exaggerated by the Dornier HM3 system, and continuous monitoring of gas exchange and appropriate oxygen administration are recommended in patients receiving regional anesthesia and sedation.

Key Words: ANESTHESIA—urologic. SURGERY—urologic. RESPIRATION—immersion.

The Dornier HM3 lithotripter is designed to disintegrate urinary calculi by underwater electromechanical shock waves generated by a spark plug at the primary focal point (F1) of an underwater parabolic mirror (Fig. 1). The reflected shock waves are concentrated in an ellipsoid area (F2) approximately 1.5 cm wide at a distance of 23 cm from the point of primary focus. The target stone is positioned at F2 by remote control under biplanar fluoroscopy. The shock waves are gated through the R-wave of the electrocardiograph and are independent of respiration. Stones in freely mobile kidneys are driven across the focal plane of the shock beam by respiratory oscillations of the diaphragm and intervening tissues. Respiratory movements must be restricted to less than 1 cm so that the stone remains within the effective limits of the beam at all phases of the respiratory cycle.

Precise control of stone movements is easily accomplished under general anesthesia, and oscillations can be restricted to 2–3 mm by a rapid, shallow pattern of intermittent positive pressure ventilation. In awake patients under regional anesthesia, stone quiescence becomes a more demanding exercise in controlled spontaneous respiration. The Dornier HM3 system is uniquely suited to studying this type of problem. Stone excursions measured on fluoroscopy provide a quantitative indication of diaphragmatic activity, whereas simultaneous measurements of gas exchange and respiratory rhythm are available through non-invasive monitoring techniques that have become an established part of contemporary standard of care. In addition, the respiratory stresses imposed by immersion exaggerate the effects of respiratory depressant agents and act as an amplifying system for drug comparisons.

This report presents a study of the mechanical contribution of the Dornier HM3 harness to control of respiratory stone excursions in awake spontaneously breathing patients under epidural analgesia. Although this physical contribution could be measured by image intensifier screening before or after immer-

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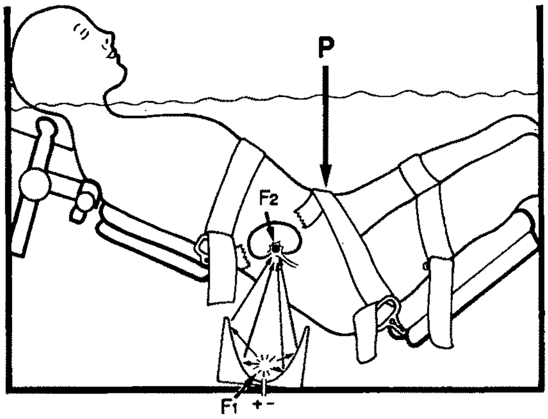

Figure 1. Diagram of the Dornier HM3 ESWL system. Underwater electromechanical shock waves generated at F1 are concentrated on renal calculi positioned by remote control to lie at the point of secondary focus F2. P indicates where hydrostatic measurements of surface abdominal pressure were made under the point of intersection of crossed restraining straps.

sion, we adopted the following indirect procedure to avoid unnecessary additional exposure to radiation.

Methods

Simultaneous recording of respiratory frequency (f), tidal volume (VT), oxyhemoglobin saturation (SaO$_2$), and end-tidal carbon dioxide (PETCO$_2$) enabled changes of respiratory movements and gas exchange to be related to the physical effects of immersion and harness restraint, as well as to the pharmacological effects of a respiratory depressant drug administered after immersion. Precise recordings of stone excursion on the Dornier image intensifier, before and after sedation, provide a measure of diaphragmatic excursion and of the correlation between reduction of tidal volume and stone excursion due to pharmacologic intervention. Assuming a similar relationship between tidal volume and stone movement before and after immersion, the contribution of immersion itself to control of stone motion can be calculated.

Protocol

Studies were carried out in 70 awake unpremedicated spontaneously breathing patients aged between 16 and 60 years, with freely mobile kidneys undergoing ESWL for renal stone. All subjects gave informed consent and institutional approval was obtained for the study. All patients were ASA physical status I or II, free of diabetes or pulmonary disease, and were fasting for 8 hours or more prior to treatment. Fluid deficits were made good by a rapid intravenous infusion of 5% dextrose in normal saline solution to a volume of 7–10 ml/kg body weight. Epidural analgesia was induced at any convenient interspace between the 8th and 12th thoracic spines. Respiratory measurements began after the establishment of epidural analgesia to a segmental level of the sixth thoracic dermatome or higher. A dilute solution of bupivacaine (0.25%) was used for epidural analgesia to avoid motor blockade of intercostal and abdominal muscles.

Respiratory frequency (f) and PETCO$_2$ were measured continuously with the use of a nasal sampling catheter and a Datex recording capnograph calibrated with two standard CO$_2$ concentrations. Arterial oxyhemoglobin saturation (SaO$_2$) was measured with the use of a Biox 3700 pulse oximeter and finger probe with a coefficient of variation of less than 0.5% for repeated steady-state readings. Baseline readings of PETCO$_2$, f, and SaO$_2$ were recorded over a period of 4–5 minutes with the subjects supine and resting quietly. The patients were then positioned in the Dornier chair. The chest strap was left loose, whereas the abdominal restraining straps were adjusted to lie over the mid-abdomen and then tightened to produce a comfortable but firm restraint. In 38 patients, surface pressure (SP) under the cross-over point of the abdominal restraining straps was measured in centimeters of water with a water-filled system consisting of a 250 ml plastic bag connected to plastic manometer tubing, and the vertical height of the water column above the abdominal wall was measured in centimeters. Mean SP was taken as the midpoint between inspiratory and expiratory readings of the fluid column. Readings of PETCO$_2$, f, SP, and SaO$_2$ were recorded over a period of 3–5 minutes with the patient in the harness before immersion. These readings were then repeated after immersion to treatment depth in the Dornier water bath. Final readings of PETCO$_2$, f, and SaO$_2$ were made after removal from the water bath with the patient lying supine and unrestrained.

The respiratory effects of harness restraint and immersion were also studied in seven unanesthetized volunteers aged between 23 and 66 years. The same sequence of measurements was followed, as described previously, but without prior fasting or administration of any drugs.

After immersion, respiratory oscillations of the target stone were measured in millimeters with use of the Dornier image intensifier screen. This visual system has a magnification of approximately two, depending on the distance of the X-ray tube from the target stone, and so measurements were halved to

Table 1. Respiratory Changes After Immersion in Dornier HM3 Water Bath and After Intravenous Midazolam (Means ± SEM)

	N	Rest Control	After Immersion	After Intravenous Midazolam	Dose of Intravenous Midazolam (mg/kg)
Respiratory frequency (breaths/min)	70	17.80 ± 0.4	21.82 ± 0.57***	19.58 ± 0.54**	0.049 ± 0.0004
SaO_2 (%)	70	97.49 ± 0.23	96.41 ± 0.3**	91.53 ± 0.56***	
$PETCO_2$ (mm Hg)	70	38.43 ± 0.41	38.43 ± 0.39	41.82 ± 0.49***	
Tidal volume (ml)	34	451.1 ± 17.10	392.9 ± 17.9***	292.7 ± 9.3***	0.045 ± 0.002
Stone excursion (mm)	34		11.46 ± 0.64	4.60 ± 0.3***	

$^{**}P < 0.01$; $^{***}P < 0.001$: significance of difference of mean from preceding value.

obtain a close approximation of true anatomical amplitude of stone movement. Measurements of stone oscillations were repeated 3–4 minutes after intravenous administration of midazolam 0.027 to 0.078 mg/kg body weight.

Measurements of f, minute volume, and VT were made in 34 patients after establishment of epidural anesthesia, before immersion, after immersion, and again 2–4 minutes after midazolam administration, with the use of a Wright spirometer and close-fitting face mask held manually in place. Typical reflex respiratory artifacts were elicited by mask contact during measurements of minute and tidal volumes and were expressed on the capnograph trace as a slight elevation of inspiratory CO_2 and $PETCO_2$. However, these artifacts were consistent for any individual subject at all measurement epochs and so were ignored in subsequent calculations.

The parameters of all three epochs were analyzed by Hotelling's T-square multivariate analysis for repeated measures and individual comparisons were performed by Bonferroni's adjusted paired *t* test, with use of statistical software from the P1D and P3D programs of the BMDP statistical package (1987). Linear regression was used to test the degree of association between changes in VT and changes in amplitude of stone movement after intravenous midazolam. All values are expressed as mean ± SEM.

Results

Increased abdominal pressure was associated with an increase in f. Harness tension before immersion increased abdominal surface pressure by 14.5 ± 0.7 cm H_2O, accompanied by an 8.8% increase in f from a rest mean of 17.8 ± 0.4 to 19.3 ± 0.9 breaths/minute. After immersion to treatment depth, abdominal surface pressure increased further to 32.9 ± 1.0 cm H_2O, and f increased to 21.8 ± 0.6 breaths/minute, a statistically significant increase of 22.6% above preharness levels. There was no significant difference between the rest f values in the supine position before immersion or after ESWL, indicating that the response to the mechanical load imposed by immersion was transient and spontaneously reversible after removal from the water bath. Values of f in the volunteers followed the same general trend as in ESWL patients given epidural analgesia, with a significant 17% increase in f during immersion and a rapid return to rest control after removal from the water bath. Changes of f, SaO_2, VT, and stone excursion are summarized in Table 1. Immersion caused no change in $PETCO_2$, but there were statistically significant decreases in SaO_2 and VT, whereas minute volume remained sustained by increases in f.

Within 2–5 minutes of administering midazolam 0.027 to 0.078 mg/kg body weight, SaO_2 decreased sharply to a second nadir of 5.0 ± 0.4% (range −1-−10.6%) below pre-immersion levels and to a total of 6.1% (range −1.5-−13.8%) below rest pre-immersion values. In 13 of 70 patients SaO_2 decreased to 88% or lower, and in three patients oxygen administration was required to increase the SaO_2 above 85%. $PETCO_2$ increased more slowly than the steep decline of SaO_2 after midazolam and reached a peak of approximately 8% above rest levels 5–10 minutes after the nadir of SaO_2 was reached. Stone movement abruptly decreased by an average of 60% within 90 seconds of intravenous midazolam. At the same time, VT decreased 25%, f 10%, and minute volume 33% below post-immersion values.

Reduction of stone excursion and VT were linearly significantly related with a correlation coefficient of 0.45 ± 0.174. The total reduction of VT imposed by

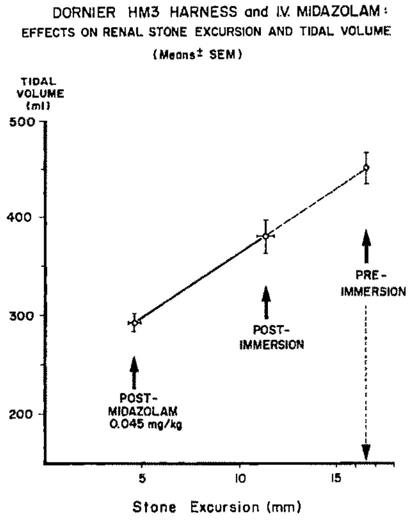

Figure 2. Effect of immersion in the Dornier HM3 apparatus and intravenous midazolam 0.045 ± 0.002 mg/kg body weight on tidal volume and renal stone excursion in 34 patients. Extrapolation to the mean ± SEM pre-immersion tidal volume of 451 ml yields a corresponding pre-immersion stone excursion of 16.6 mm.

both immersion and midazolam amounted to a significant 35% decrease below rest pre-immersion levels. Assuming a corresponding reduction of stone excursion, the calculated pre-immersion value for stone oscillations would have been 16.6 mm as shown in Figure 2. From Table 1, it can be seen that of the total reduction of stone movement from this calculated value of 16.6 mm, midazolam contributed 57% and immersion contributed 43%.

Discussion

Our initial assumption of a proportional relationship between changes of VT and stone oscillation on immersion and after benzodiazepine administration appears to be supported by the data. The range of total changes in VT measured in this series, between 8 and 360 ml (average 158.4), was small enough to fall on a linear part of the normal compliance curve relating lung volume to intrathoracic pressure changes. In this model, the diaphragm was likely to be the principal generator of pressure as well as the reason for stone movement, because rest VT appeared to be entirely abdominal, and once in the harness, lower rib activity was partially splinted by the crossed restraining straps. The correlation coefficient of 0.45 between reduction of VT and stone excursion after midazolam indicates a significant linear relationship between the two parameters in the post-immersion phase. Extrapolation of this linear relationship to pre-immersion VT yields a corresponding value of 16.6 mm for rest stone movements that is remarkably close to the figure of 15.6 mm reported for rest diaphragmatic excursions measured by ultrasound in unanesthetized subjects (1).

Although our patients were reclining at a shallow depth in the Dornier water bath, the actual pressure exerted on the surface of the abdomen by the Dornier restraining straps, in excess of 30 cm H_2O, was approximately equivalent to the hydrostatic pressure on the upper abdomen when standing unrestrained in water up to the neck. The respiratory and cardiovascular effects of immersion in thermoneutral water to a level of the chin have been studied extensively in the erect and sitting postures and are well understood (2–8).

These effects include a decrease in vital capacity (VC) of between 4 and 60% (2–4), reduction in functional residual capacity (FRC) of 30% (5), and increase in intrathoracic blood volume of approximately 0.7 liters (5–7), accompanied by decreased intrapleural pressure, (6) increased elastic work of breathing (4) and a compensatory 15% increase in respiratory rate, and a 9% decrease in PaO_2 due to unfavorable changes of ventilation-perfusion ratios in the lung (8).

Our data reflect closely comparable changes in the parameters measured. The slight decrease in SaO_2 on immersion represents a leftward shift along the oxyhemoglobin dissociation curve equivalent to a decrease in PaO_2 of 5–10 torr, whereas the 23% increase in f and 13% decrease in VT reflect the normal response to increased elastic work of breathing that accompanies a decrease in FRC (9,10).

In practical clinical terms, the abrupt change to a rapid, shallow pattern of respiration on immersion represents a compensatory reflex adjustment to increased work of breathing that is favorable to the maintenance of an adequate minute volume as well as to the technical requirements of ESWL, because shallow movements of the diaphragm reduce respiratory oscillations of the target stone and increase the ratio of target-to-tissue shock-wave energy.

The penalty incurred by immersion is a ventilatory system stressed by an increased elastic work load and made more susceptible to the pharmacological effects of centrally or peripherally acting depressants including the benzodiazepines. The second sharp decrease in SaO_2 after a modest dose of midazolam (0.045 mg/kg body weight) was about twice as great as in non-immersed patients with epidural blockade given similar doses of midazolam (Bromage, unpublished data) and reflects the very tangible respiratory handicap imposed by immersion. Although respiratory responses to benzodiazepines are variable, the combined effects of immersion and small doses of intravenous midazolam caused dramatic decreases in SaO_2 to potentially dangerous levels below 89% saturation in one of five of our patients, and to below 85% of SaO_2 in 4% of apparently normal individuals.

In conclusion, the data presented reveal the Dornier system to be a device that limits respiratory movements of target stones in awake, spontaneously breathing subjects. At the same time, it demonstrates the intrinsic respiratory hazards of the system in relatively lightly sedated patients under regional analgesia. The effects of increased elastic work of breathing, central sedation, and absence of pain to augment respiratory drive combine to induce potentially dangerous levels of hypoxia in a small proportion of normal subjects breathing room air. These results emphasize that safe practice requires close surveillance and continuous monitoring of gas exchange when sedative agents are administered to patients under regional anesthesia for ESWL in the Dornier HM3 system. In the absence of such safeguards, supplementary oxygen should be administered as a routine precaution.

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SPECIAL ARTICLE

Principles of Pulse Oximetry:

Theoretical and Practical Considerations

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Key Words: MEASUREMENT TECHNIQUES—pulse oximetry. OXYGEN, MEASUREMENT—pulse oximetry.

Continuous monitoring of arterial oxygen saturation with a pulse oximeter is rapidly becoming a standard of anesthesiology practice (1). Because of the tremendous potential market, more than 20 manufacturers now produce pulse oximeters. As one might expect, there have been many unsubstantiated claims and couterclaims regarding those features and capabilities that distinguish one oximeter from another. The purpose of this communication is threefold: (a) to review the underlying principles of pulse oximetry and the limitations they impose, (b) to provide a basis for assessing pulse oximeters to be used in a particular application, and (c) to make available the results of a comparative evaluation of nine widely marketed pulse oximeters (Table 1).

Basic Principles

Pulse oximeters provide instantaneous, in vivo measurements of arterial oxygenation by determining the color of the blood between a light source and a photodetector. To be able to distinguish between two species of hemoglobin—i.e., oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb)—it is necessary to measure absorption at two different wavelengths (Fig. 1). This is accomplished by using a light source that consists of two different light emitting diodes (LEDs), one emitting red (≈660 nm) and the other infrared (≈940 nm) light. Oxyhemoglobin absorbs less red light than deoxyhemoglobin, accounting for its red color; at infrared wavelengths, the opposite is true.

Each LED is illuminated in turn at frequencies that vary by manufacturer but may be as high as several hundred Hz. In some designs, a third phase of both LEDs off (Fig. 2) allows the oximeter to detect and compensate for any extraneous light (i.e., not coming from the LEDs) that might cause interference by striking the photodetector (2). The photodetector, which is positioned on the opposite side of the tissue bed being monitored (e.g., finger, ear, nose), cannot distinguish between different wavelengths. Therefore, at any given time, the software of the oximeter assumes that all of the light reaching the photodetector has a wavelength corresponding to that of the concurrently illuminated LED.

During each cardiac cycle, light absorption by tissue beds varies cyclically (Fig. 3): during "diastole," absorption is caused by venous blood, tissue, bone, and pigments (melanin, nail polish, etc.). During "systole," there is an increase in light absorption that pulse oximeters assume to be created by the influx of arterialized blood into the tissue bed. The oximeter then determines the difference between background absorption during "diastole" and peak absorption during "systole" at both red and infrared wavelengths; these changes correspond to the absorption caused by arterialized blood. Oxygen saturation determines the red:infrared absorption ratio (v.s.); thus the red:infrared ratio of these pulsatile differences can be used to compute the pulse oximeter reading (SpO_2), which is an estimate of arterial oxygen saturation (SaO_2).

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Table 1: Alphabetical Listing of the Pulse Oximeters Evaluated

1. Catalyst MiniOx 100: Catalyst Research Division, Mine Safety Appliances Corporation, 3706 Crondall Lane, Owings Mills, MD 21117
2. Criticare 501+: Criticare Systems, Incorporated, P. O. Box 26556, Milwaukee, WI 53226
3. Datascope Accusat: Datascope Corporation, 580 Winters Avenue, Paramus, NJ 07653
4. Invivo 4500: Invivo Research Laboratories, 3061 W. Albany, Broken Arrow, OK 74012
5. Nellcor N-200: Nellcor, Incorporated, 25495 Whitesell Street, Hayward, CA 94545
6. Ohmeda 3700: Ohmeda-Biox Division BOC, 4765 Walnut Street, Boulder, CO 80301
7. PhysioControl Lifestat 1600: PhysioControl Corporation, P. O. Box 97006, Redmond, WA 98073
8. SARA Oximetry System: SARA Division PPG Biomedical Systems, Incorporated, 897 Fee Fee Rd., St. Louis, MO 63043
9. SensorMedics Oxyshuttle: SensorMedics Corporation, 1630 S. State College Blvd., Anaheim, CA 92806

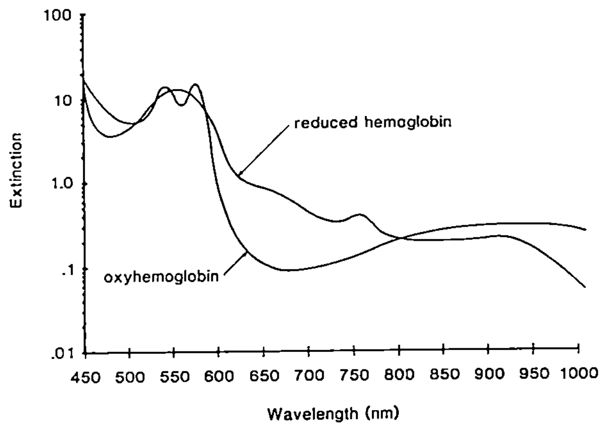

Figure 1. Light absorption (extinction) as a function of wavelength for oxyhemoglobin (HbO_2) and reduced hemoglobin (Hb). Reproduced from (2) with permission.

In addition to absorption by hemoglobin, refraction and reflection (i.e., scattering) of the light beam also occur within tissue beds. Scattering at the interface of red cells and plasma may account for more than 50% of the 660 nm absorption by whole blood (3), while scattering at the tissue-bone interface may account for calibration differences between ear and finger pulse oximeter probes (4). As a result, it is necessary for manufacturers to calibrate pulse oximeters using empirical, in vivo data (Fig. 4). Because it is difficult to obtain reliable human calibration data at saturations less than 70%, the accuracy of pulse oximeters tends to decrease during extreme hypoxemia (5).

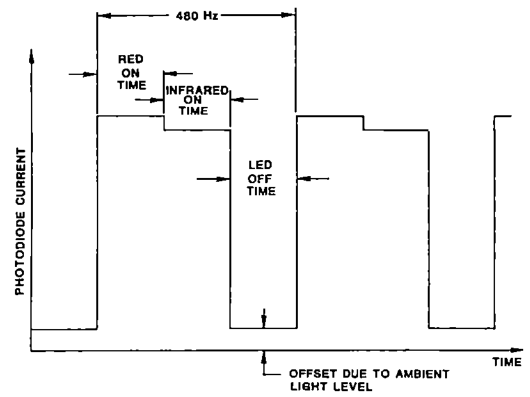

Figure 2. LED on-off cycle for a typical pulse oximeter (Ohmeda 3700). Reproduced from (2) courtesy of Ohmeda.

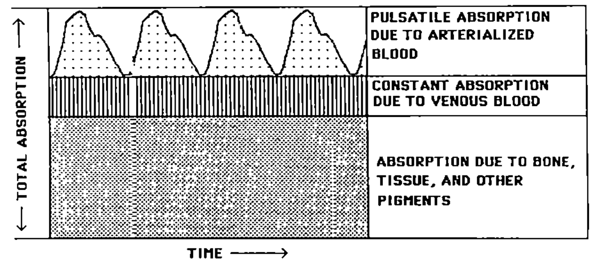
PULSATILE ABSORPTION DUE TO ARTERIALIZED BLOOD
CONSTANT ABSORPTION DUE TO VENOUS BLOOD
ABSORPTION DUE TO BONE, TISSUE, AND OTHER PIGMENTS
TOTAL ABSORPTION
TIME

Figure 3. Components of light absorption by a tissue bed as a function of time.

Physiologic Factors

Because their operation is based on the same principles, all pulse oximeters are subject to certain physiologic limitations in addition to the above technical limitations. For example, detectable plethysmographic pulsations are necessary to enable an oximeter to distinguish between light absorption by arterial blood and the background absorption associated with venous blood and tissue constituents. Thus, oximeters may give unreliable readings or cease functioning entirely when peripheral arterial pulsations are reduced or absent. For instance, patients profoundly vasoconstricted because of hypothermia, hypovolemia, or cardiogenic shock may have inadequate pulsatile flow in the finger or other peripheral sites to allow pulse oximeters to function properly. A related observation is the fact that acute changes in arterial saturation may not be reflected by finger pulse oximeters for as long as 30 seconds (4). When probes are placed on the ear, however, pulse oximeters respond within 5–10 seconds, making earlobe measurements more useful in situations where the oxygen saturation of arterial blood (SaO_2) may change acutely. Since readings from pulse oximeters on the ear correspond closely with in vitro measurements made of radial arterial blood, it appears that the delay in finger pulse oximetry readings may be related to the time

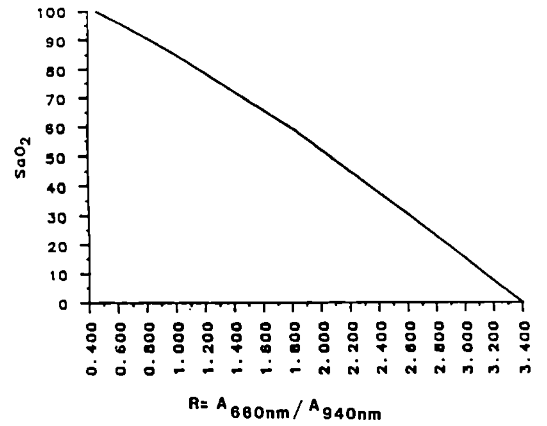

Figure 4. Empirically determined calibration curve showing SaO_2 as a function of red:infrared absorption ratio. From (2) courtesy of Ohmeda.

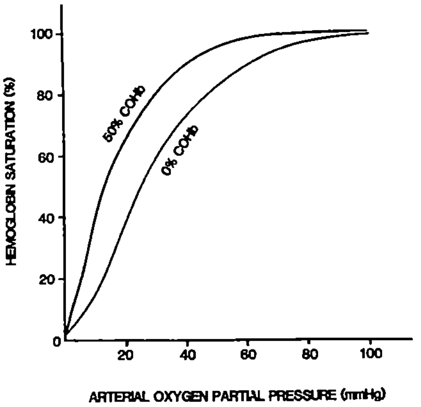

Figure 5. Oxyhemoglobin dissociation curves for adult hemoglobin in the absence and presence of 50% carboxyhemoglobin (COHb).

required to "arterialize" the pulsatile finger pulp blood flow. Increasing blood flow by warming the hand decreases the time delay, supporting this hypothesis (6).

Because pulse oximeters measure oxygen saturation rather than oxygen tension, their readings must be interpreted accordingly. For instance, when the F_IO_2 is high, measured oxygen saturation may remain normal despite a significant deterioration in pulmonary gas exchange. This is a result of the sigmoid shape of the oxyhemoglobin dissociation curve (Fig. 5): a 300 mm Hg increase in the alveolar-arterial oxygen tension difference (e.g., a decrease in PaO_2 from 500 to 200 mm Hg) results in less than a 1% decrease in SaO_2. Therefore, determination of PaO_2, either from arterial blood or transcutaneously (7), will provide an earlier indication of deteriorating pulmonary function. However, since delivery of oxygen to the tissues is proportional to arterial oxygen saturation, pulse oximeters will detect changes in pulmonary gas exchange before tissue oxygenation is impaired. Although pulse oximetry is less sensitive to developing ventilation-perfusion mismatching than arterial blood gas determination, this is offset by the ability of the pulse oximeter to provide continuous, rather than intermittent, data.

Sources of Interference

Pulse oximeters are subject to two types of interference. Intrinsic interference results from factors within the patient that artifactually affect the absorption of 660 or 940 nm light. All currently manufactured oximeters use these same wavelengths; therefore, they would be expected to respond similarly to this type of interference. Furthermore, because it is associated with normal plethysmographic pulses, the presence of intrinsic interference cannot be indicated by artifact detection algorithms or pulse waveform displays. Conversely, extrinsic interference results from factors external to the patient which artifactually alter light transmission between the LEDs and photodetector (e.g., patient movement) or interfere with the very weak electrical signal (typically 1/10 to 1/100 as strong as an ECG signal) developed by pulse oximeter probes. As a result, the oximeter is unable to determine accurately which electrical signals correspond to arterial pulsations. Because extrinsic interference can be reduced or eliminated by engineering modifications, oximeters vary considerably in their ability to reject it, as discussed below.

Intrinsic Interference

Because current pulse oximeters use only two wavelengths, they are able to distinguish between only two different species: Hb and HbO_2. Clinically, this limitation does not present a problem if the concentrations of methemoglobin (MetHb) and carboxyhemoglobin (COHb) are less than a few percent; however, when they are present in higher concentrations, oximeters may display erroneous and potentially dangerous data.

The effect of dyshemoglobins on pulse oximeter readings depends on how their light absorption compares to that of Hb and HbO_2 at 660 and 940 nm. COHb, for instance, absorbs almost identically to HbO_2 at 660 nm. Therefore, oximeters respond to COHb as if it were HbO_2, and the pulse oximeter reading (SpO_2) is the sum of COHb and HbO_2 (8) (i.e., if a patient had 90% HbO_2, 7% COHb, and 3% Hb, a pulse oximeter would read SpO_2 = 97%).

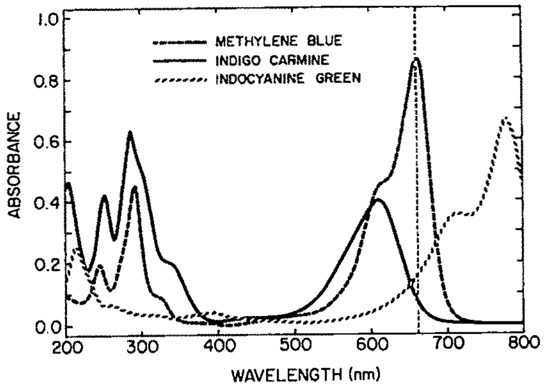

Figure 6. Absorbance spectra of methylene blue, indigocarmine, and indocyanine green. Note that methylene blue has a strong absorption peak at 660 nm, accounting for its significant effect on pulse oximeter readings. From (11) with permission.

In patients with significantly elevated HbCO (e.g., cigarette smokers, fire victims), this is dangerous for two reasons: 1) the pulse oximeter overestimates the oxygen content of arterial blood and 2) the presence of HbCO shifts the oxyhemoglobin dissociation curve to the left (increased oxygen binding), thus decreasing oxygen delivery to the tissues (Fig. 5).

Methemoglobin has approximately the same absorption coefficient at 660 and 940 nm (9). Oximeters interpret this 1:1 absorption ratio as corresponding to an SaO_2 of 85% (Fig. 4). Therefore, in the presence of methemoglobin, pulse oximeter readings correspond to a weighted average of the O_2 saturation of the hemoglobin available for transport $S_{avail}O_2 = HbO_2/(HbO_2 + Hb)$ and 85% (10) (i.e., $SpO_2 = Fmet \times 85\% + (1-Fmet) \times S_{avail}O_2$). Elevated levels of methemoglobin may occur in patients exposed to drugs such as amyl nitrite or nitroglycerin. In conclusion, if significant fractions of met- or carboxyhemoglobin are suspected, either on the basis of history or because of discrepancies between oximeter readings and blood gas results, in-vitro measurement of COHb and MetHb with a multi-wavelength CO-oximeter must be performed before pulse oximeter readings can be interpreted.

There have been numerous reports of erroneous pulse oximeter readings following the intravenous administration of dyes for diagnostic purposes (11–13). Figure 6 indicates why this occurs: Methylene blue, and to a lesser extent indocyanine green have significant absorption bands at 660 nm. Oximeters interpret increased 660 nm absorption as resulting from decreased HbO_2 (simply stated, the blood appears more blue, implying a lower oxygen saturation). Therefore, an artifactually low saturation is displayed. This effect is short-lived (5–10 min) because of redistribution—when dye has redistributed to the non-pulsatile tissue compartment, there is no further effect on pulse oximetry readings (14).

Because light absorption by nail polish is constant rather than pulsatile, it would not be expected to affect pulse oximeter accuracy. However, opaque coatings may significantly decrease light transmission, rendering oximeters inoperative. Furthermore, certain blue nail polishes have strong absorption bands in the vicinity of 660 nm; as a result, falsely low oximeter readings may occur (15).

Detection and Rejection of Extrinsic Interference

The ability of pulse oximeters to function in the presence of patient motion, electrocautery, or other extrinsic interference depends upon engineering design considerations. To accurately evaluate the relative merits of different oximeters, it is necessary to perform a comparative evaluation under controlled conditions. While our results only include the oximeters listed in Table 1, the principles we will discuss apply to any pulse oximeter one might wish to evaluate.

Patient motion interferes with pulse oximeters by two mechanisms. First, depending upon the mass and shape of the oximeter probe, the orientation of the probe with respect to the finger tends to change during motion. For this reason, flexible, adhesive probes, which are taped in place, tend to be less susceptible to motion artifacts than clip-on probes. A second source of interference due to motion is the current which is induced in the connecting cable when it moves with respect to the earth's magnetic field.

We conducted a two-phase evaluation of motion artifact susceptibility. First, after obtaining stable oximeter readings with subjects breathing room air, we asked them to vigorously wiggle their fingers. We observed the oximeters for change in saturation reading, loss of pulse signal, and the presence of an artifact message. We found that oximeters varied considerably in their susceptibility to this type of artifact. Oximeters with large, massive probes (e.g., PhysioControl, Invivo) were more susceptible to motion artifact than those with lightweight probes (e.g., SensorMedics, Criticare). Some indication that interference was present, such as an artifact message (Invivo) or clearly abnormal waveform display (Ohmeda), was helpful in interpreting the validity of oximeter data under these conditions.

To determine if the oximeters were able to update their readings during motion (as opposed to merely displaying previously obtained data), we first had our volunteers breathe a hypoxic gas mixture until SpO_2 was 90%; we then asked the subjects to wiggle their fingers while discontinuing the hypoxia. After waiting 30–40 seconds (corresponding to the physiological delay in finger pulse oximetry, v.s.) we found that most oximeters returned quickly to their pre-hypoxia readings. One oximeter (PhysioControl) was unable to track these changes and read 0% oxygen saturation for approximately 15 sec before recovering.

A novel approach to the motion artifact problem is synchronization of acquisition of data by the pulse oximeter with the ECG R-wave (Nellcor). However, we found that the oximeter may synchronize with the ECG artifact generated by motion or shivering, resulting in erroneous readings. Furthermore, with this system, the pulse rate displayed by the oximeter is necessarily equal to the pulse rate shown by the ECG monitor; therefore, when using this system, equality of the pulse rates indicated by the ECG and the oximeter should not be used as an indication that the displayed saturation data are valid.

Pulse oximeters also differ considerably in their ability to function in the presence of electrosurgical interference. To quantitate these differences, we cauterized a piece of steak. A volunteer was included as part of the ground-return circuit, and the active electrode wire was in close proximity to the oximeter probe and cable. For each oximeter, we determined the maximum cutting and coagulating current that could be used before interference occurred. Special shielding and suppression circuitry enabled one oximeter (Datascope) to be totally immune to cautery interference, both in the laboratory and in the operating room. Others (Criticare, Nellcor, PhysioControl, and SARA) performed well in the laboratory, where our volunteers had strong pulse signals. However, in patients with weak pulse signals, all of these units give erroneous readings during electrosurgery. A different design philosophy (Ohmeda) gives an error message and stops acquiring data whenever cautery interference exceeds a threshold which is independent of pulse signal strength. Therefore, in patients with strong signals, this oximeter stops acquiring data and gives an error message while others (Criticare, Nellcor, and PhysioControl) continue to function normally. However, because data acquisition is discontinued, the Ohmeda design avoids erroneous readings and false alarms during electrocautery in patients with weak pulse signals.

There have been several case reports regarding oximeter interference from overhead xenon-arc surgical lamps (16,17), the output of which tends to flicker. Depending upon the relationship between the sampling frequency of the pulse oximeter (v.s.) and the flicker frequency of the light source, pulsatile interference at physiological frequencies may develop. (Recall that the photodetectors are sensitive to light from any source.) Should this occur, the oximeter reading may be erroneously high or low. There are several ways this problem can be minimized. First, good probe design may prevent external light from reaching the photodetector (Criticare, SARA). Other oximeters (Invivo, Ohmeda), while more sensitive to extrinsic light sources, indicate that interference is present with an error message or abnormal waveform (Fig. 7); should this occur, the problem is easily rectified by covering the oximeter probe with an opaque drape. Unfortunately, oximeters that lack both waveform and diagnostic message displays (Nellcor) give unpredictably high or low readings during such interference, without any indication of the presence of interference; ECG synchronization does not appreciably reduce the susceptibility to this type of interference. Indeed, a predominance of the reports describing false oximeter readings in the presence of apparently normal function have been with such units (16,18).

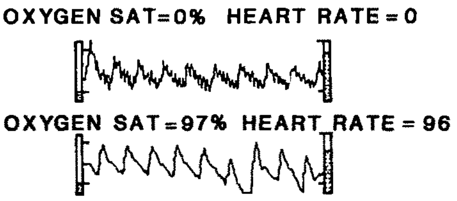

Figure 7. Pulse oximeter (Invivo 4500) waveform showing interference from xenon arc surgical lamp. The lower trace shows a normal waveform for comparison.

Signal Verification

As we have discussed, there are numerous sources of pulsatile interference that may adversely affect pulse oximeter operation (18). A pulse waveform display enables the operator to determine whether the oximeter is detecting valid pulses or interfering signals. By analogy, an arterial catheter without a waveform display might give accurate pressure readings under most conditions, but erroneous readings resulting from artifact would be difficult to recognize. Normalization of the waveform amplitude (Ohmeda, Invivo) allows weak signals to be visualized more easily.

An indication of the absolute signal strength (Catalyst, Datascope, Invivo, Ohmeda) is helpful for two reasons: First, full strength signals suggest that displayed readings are more likely to be reliable, since the oximeter is not functioning near the limits of its performance. Second, signal strength serves as an indicator of relative peripheral perfusion. This can be helpful in the diagnosis of intraoperative hypotension: a full strength signal suggests that peripheral perfusion is adequate, while low strength signals imply vasoconstriction and low cardiac output. Bouncing dot displays (Invivo, Nellcor, PhysioControl) do not, by themselves, reliably indicate signal strength or validity.

Built-in real-time displays of signal strength and pulse waveform (Ohmeda) are most convenient in a majority of applications. However, it is also possible to display oximeter waveforms on a compatible monitor in the operating room (e.g., SARA, Datascope); this is most suitable for those who already own specific monitors and do not plan to use the pulse oximeters independently. Finally, one oximeter (Invivo) has a small, onboard printer that will print pulse strength and waveform information on request; however, there is a time delay, and continuous printing would waste a considerable amount of paper.

Status Messages

In addition to waveform displays, many oximeters provide messages to inform the operator of their functional status. The utility of these messages varies considerably among oximeters. Some units give a wide variety of distinct messages such as "no probe connected," "probe off patient," and "insufficient light detected" (Catalyst, Datascope, Invivo Ohmeda). Flashing logos on liquid crystal screens (Criticare, SARA, SensorMedics) convey similar information but may be more difficult to interpret since a single logo may be used for multiple problems. The least desirable systems indicate "pulse search" for just about any abnormal situation, which is a clear disadvantage (Nellcor, PhysioControl).

Pulse Beep

All pulse oximeters indicate that they have detected a plethysmographic pulse by emitting a beep coincident with each heartbeat. The best design, which is shared by most of the oximeters (except for Catalyst, Criticare, SARA), makes the pitch of this beep proportional to SpO_2. In this way, the operator can be aware of changes in SpO_2 before alarm limits are violated, even if the digital read-out of the oximeter is not in constant view.

Alarms

Ideally, a pulse oximeter should have an alarm that is distinct and not easily confused with other alarms or sounds in the operating room. The most distinctive alarms sound like a video game (Catalyst) or like two-tone sirens (Invivo, SensorMedics). In contrast, some oximeters (e.g., SARA, Criticare) have alarms indistinguishable from the beep emitted from a radiopager. The best alarm sound is a matter of personal preference and depends to a large extent on the other equipment with which the oximeter will be used.

The ability to disable specific alarms is useful, especially when patient position, site of operation or patient anatomy dictate that the pulse oximeter probe be placed on the same hand as the blood pressure cuff. In this situation, the ability to avoid annoying false alarms during BP cuff inflation without disabling all of the alarms is important. Turning off the low pulse rate alarm of some oximeters (Ohmeda) prevents them from alarming when a BP cuff is inflated for up to 30 seconds. ECG synchronization (Nellcor) allows the heart rate display to remain accurate despite BP cuff inflation; this prevents false "low heart rate" alarms during BP determination. For most oximeters, however, the only way to prevent alarms during BP cuff inflation is the dangerous practice of disabling all alarms.

Ease of alarm adjustment and retention of previously set default values are other important considerations. Ideally, one should be able to set limits in either an up or down direction, so that if the desired value is missed, it is not necessary to go through the entire cycle again. Some oximeters retain previous alarm limit settings either in memory (Invivo) or on thumbwheels (SensorMedics). However, most revert to their factory preset values when the oximeter is turned off. Continuous display of alarm settings is another advantage. Some oximeters show alarm thresholds only when a menu button is pressed (Nellcor, Invivo).

The ease of adjusting the pulse beep and alarm loudness differs significantly among units. Some use knobs like a radio (Datascope), while others use dedicated buttons (Ohmeda, SensorMedics). A menu format may be less convenient (Catalyst, Invivo). When alarms are completely disabled, a message should be displayed (PhysioControl, Nellcor, SensorMedics). Systems where alarms are off until manually activated (SensorMedics), or where it is easy to accidentally disable alarms (PhysioControl), may be a disadvantage.

Accuracy

Most manufacturers specify that their oximeter readings can be expected to have a 2–3% standard deviation in the 70–100% saturation range. To verify these claims, we performed an evaluation of the accuracy of

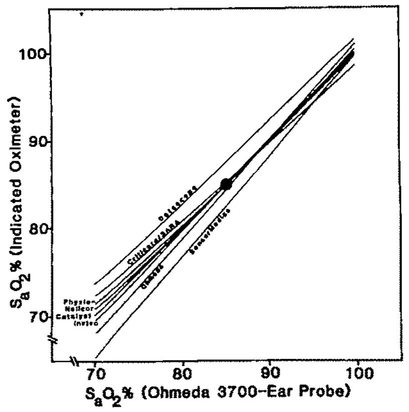

Figure 8. Saturation readings from nine pulse oximeters with finger probes vs. simultaneous readings from an Ohmeda 3700 pulse oximeter/ear probe combination that we had previously calibrated against a CO-oximeter (4). The "Ohmeda" curve refers to a new, production model Ohmeda 3700/finger probe combination, and therefore does not correspond to the line of identity. Note that the Datascope reads 2–3% high and SensorMedics reads 1–4% low in the 70–100% saturation range (see text).

oximeters listed in Table 1. Eight subjects inhaled mixtures of nitrogen in oxygen to obtain arterial oxygen saturations between 70 and 100%. Prior to each measurement, we ascertained that the subjects had stable end-tidal oxygen concentrations for one minute to guarantee steady state conditions. For reference, we used the Ohmeda 3700 with ear probe, functioning in the fast (3-sec averaging) mode; we previously calibrated this oximeter against in vitro measurements with a Corning 2500 CO-oxmeter (4).

All the oximeters we evaluated had an extremely tight correlation with the reference standard ($r > 0.98$, $s < 3\%$). The slope of the regression lines varied from 0.95 to 1.21 among the various units we tested (Fig. 8); however, the resulting errors were not significant in the 70–100% saturation range. One oximeter (Datascope) gave readings 1–3% higher than any other oximeter throughout the 70–100% range. Although undesirable, this degree of bias is unlikely to be clinically significant.

These close correlations and tight limits of the regression line tend to overstate the predictive accuracy of pulse oximetry. Based both on our data and that provided by the manufacturers, the 95% prediction limits of a single pulse oximeter reading are ±6%: i.e., there is a 95% probability that an oximeter reading of 90% corresponds to an arterial saturation between 84 and 96%. Differences between units are often smaller than the intra-unit variability, both for sequential measurements on the same individual and for measurements on different individuals. It appears that this variability results from limitations inherent in transcutaneous in vivo measurements of oxygen saturation. These include scattering of light by blood cells and tissue components, shunting of light around the pulsatile capillary bed, and variability in the wavelengths of LEDs.

Figure 1 demonstrates that the absorbance of HbO_2 changes dramatically at wavelengths less than 650 nm. Since there may be as much as ±15 nm variability in the center wavelength of LEDs from the same supplier (2), oximeter manufacturers must determine the emission wavelength of each LED and either (a) use only those LEDs the emission of which falls within a specified tolerance, or (b) adjust the internal algorithm of the oximeter to correspond to the measured wavelength of each individual LED (which is encoded in the probe and sensed by the oximeter). LED wavelengths also vary slightly with temperature; however, compensation for this effect (PhysioControl) does not appreciably improve oximeter performance.

Despite different approaches to these problems, current pulse oximeters do not differ appreciably in their accuracy; therefore, accuracy should not be an overriding issue in the choice of an oximeter. The important consideration is that an oximeter reliably indicates developing hypoxemia before harm comes to the patient; all the units we tested achieve that goal.

Physical Characteristics

The design of a pulse oximeter helps determine how easily it will adapt to clinical use. For instance, a horizontally oriented oximeter (Catalyst, Invivo, Nellcor, Ohmeda) can be conveniently placed beneath or above existing monitoring equipment, while vertically oriented oximeters (Datascope PhysioControl) may be placed adjacent to other equipment. Some oximeters (SensorMedics) can be mounted on an i.v. pole. The controls should be readily accessible; the presence of some controls at the rear (Catalyst, SensorMedics) or on the bottom (Ohmeda) of the oximeter is a distinct disadvantage. External power transformers (Criticare, SARA, SensorMedics) decrease the weight of the oximeter but may cover two outlets when plugged in; they can also break if dropped. All the pulse oximeters we evaluated have internal batteries that allow the unit to operate for between 30 minutes and 12 hours before recharging. With one exception (Catalyst), batteries are recharged whenever A.C. power is connected. All of the pulse oximeters we tested passed standard leakage tests. Electrically isolated input amplifiers (e.g., Nellcor, Invivo) offer an additional safety margin in situations where probes may be submerged in water (e.g., lithotripter baths). The other oximeters depend on the integrity of the plastic or silastic case of the probes to insure patient isolation. However, even if the insulation fails, the hazard would be minimal in view of the low voltages present in the oximeter probe.

Most probes are attached to the oximeter by a simple cable. However, one design (Nellcor) has a cable-mounted preamplifier box that must be placed near the patient because the wire which attaches the probe to the preamplifier is short. Unfortunately, this box has a tendency to fall on the floor, and the DB-9 connector between the probe and the preamp uses a friction fit that tends to become loose with age.

Screen readability is another important concern. There are two common display types: Liquid crystals offer low battery drain but may be hard to read, particularly if not back-lit. Their contrast depends on the viewing angle; some units can be adjusted to improve their visibility from different positions (Ohmeda). Light emitting diode (LED) displays are easier to read but are invisible through some protective glasses used with CO_2 lasers. The best display readability was obtained with large, bright LEDs (Invivo, PhysioControl).

Probe Design and Selection

In many applications, it is most convenient to apply a pulse oximeter to the finger; therefore, all pulse oximeters are equipped with finger probes as standard equipment. There are many different finger probe designs: LEDs embedding in silastic cushions (Nellcor, Invivo) are the most comfortable; however, because this design is bulky, it increases the susceptibility to motion artifact (v.s.). Hard plastic (Ohmeda, Criticare, SARA) and foam-lined sensors are less bulky, but are more likely to slide off the finger. A circumferential design (Datascope) may preclude use in people with extremely large fingers (although we found that even our largest patients' little fingers fit easily into this probe).

It is often beneficial to tape oximeter finger probes into place, especially when they will be inaccessible during surgery. Some finger probes (Datascope, Ohmeda) provide a plastic sleeve specifically for this purpose. It is important to avoid taping other probes in such a way as to increase the pressure with which they compress the finger because excessive pressure may cause pulsatile venous congestion resulting in falsely low SpO_2 readings.

In addition to standard, slide-on finger probes, many manufacturers provide a selection of tape-on probes. These maybe disposable (Nellcor) or reusable (Catalyst, Datascope, Ohmeda, SensorMedics) and are designed to be affixed to the finger with a variety of double-stick tapes and wraps. They are frequently suitable for pediatric use, in which case they may be taped to the palm or sole. Because they maintain a more constant orientation with the monitoring site than standard finger probes, tape-on probes are less susceptible to motion artifact. However, they are not as well shielded from ambient light sources as the slide-on design, increasing the risk of interference (v.s.). Probes designed for single-patient use should not be reused, since stray adhesive on the optical surfaces may cause erroneous readings (19); therefore, the cost of purchasing a new probe (approximately $10.00) for each patient must be considered.

Many manufacturers also provide clip-on probes, which are suitable for application to the earlobe or tongue; these are especially useful in cases where the arms are inaccessible, peripheral perfusion is poor, or a rapid response to changes in oxygenation is critical (v.s.). Rubbing the ear with alcohol or a small dab of nitroglycerin ointment appreciably increases earlobe perfusion, improving pulse oximeter performance. Stabilizing devices such as headbands or around-the-ear loops (Ohmeda) are especially useful when patients are moving.

Price

List prices of pulse oximeters range from $1800 to $6000. However, discounts are widely available, and it should be possible to purchase a top-of-the-line unit for under $4500. On a per-patient basis, the difference in cost of different oximeter models is minimal. Therefore, we do not believe that price should be a major consideration in deciding which oximeter to purchase.

Future Trends

Since pulse oximetry is a young field, it is evolving rapidly. In fact, several manufacturers have significantly upgraded their software and hardware since Table 2 was compiled in December, 1987. One recently-introduced oximeter (Catalyst MiniOx IV) is small enough to fit in a pocket, and will operate for over 90 hours on a single 9-volt battery. Another (Lawrence Medical Systems) works by light reflection rather than light transmission; this allows probes to be placed on flat body surfaces such as the forehead and chest. Further in the future, engineers are planning oximeters that will operate at multiple wavelengths, enabling them to detect and compensate for the presence of dyshemoglobins and dyes (v.s.).

It is impossible to recommend a single pulse oximeter as being best for all applications. Instead, we recommend that Table 2 be used as a guide for determining which pulse oximeter will be best for one's own, specific purposes. When testing an oxim-

Table 2. Results of Evaluation of Nine Currently-available Pulse Oximeters, Listed in Order of Estimated Overall Performance. Oximeters in the Upper Group were Judged to Perform Significantly Better than those in the Lower Group

	Weight (kg)	Error (bias) @ 85%	Physical Design	Screen Readability	Status Messages	Control Layout	Pulse Indicator	Pulse Sound	Alarm Sound	Alarm Features	Alarm Setting	Weak Sgnl. Performance	Cautery Rejection	Motion Rejection	Xenon Arc Lamp	BP Cuff	Probes (adult)	Probes (pediatric)	Portable Use	Trending	Averaging Intervals
Ohmeda 3700	3.9	−0.50	++	0[d]	++	++	++	++	−	+	+	++	+	0	+	++	+	+	0	+	3–6
Invivo 4500	3.0	−0.05	+	++	++	+	0	++	++	++	++	+	0	−	+	−−	+	N/T	+	++	3–12
Nellcor N-200	3.6	+0.41	0[b]	+	−−	+	−	++	0	+	++	+[h]	+	+[i]	−−	+	++	++	−	+	3–15
Datascope Accusat	4.5[a]	+2.41	−	+[e]	++	++	+[g]	++	+	++	+	+	++	++	0	−−	−	−−[j]	−	0	Auto
Criticare 501+	0.5	+0.81	0[c]	0	0	+	−−	−−	−−	−	−	+	+	++	+	−−	+	+	++	0	Auto
PhysioControl 1600	6.1	+0.07	0	++	−−	++	−	++	+	−	+	0	+	−−	N/T	−−	0	++	−−	−	Auto
SARA Oximeter	2.0	+0.81	−[c]	0	0	+	0[g]	−−	−−	−	−	+	+	++	+	−−	+	+	N/A	+[k]	Auto
SensorMedics	2.8	−1.50	−−[c]	−−	0	−[f]	0	++	++	−−	++	+	−	++	−−	−−	+	−	+	+	0–30
Catalyst MiniOx 100	4.5	−0.56	+	++	+	−−[f]	0	−	++	0	+	−	−	−	0	+	−	+	−	−	Auto

Notes:
a—6.4 kg with battery
b—clumsy junction box
c—external power supply
d—view angle control under unit
e—status message screen (LCD) hard to read
f—power switch on rear
g—when used with external monitor
h—slight improvement with ECG synchronization (C-lock)
i—total body movement (e. g. shivering) may fool C-lock
j—temperature may exceed 38° C
k—when used with SARA system

++ + 0 − −−
best worst

N/A = Not Applicable

N/T = Not Tested

eter, try it on many different types of patients and in many different settings (in the operating room, recovery room, intensive care unit, etc.). Determine how well the oximeter responds in the presence of peripheral vascular disease, electrosurgical interference, and patient motion. Other questions to be considered include: Where will the oximeter fit? How convenient are the probes? Can they be taped in place? After these factors have been considered, you will have the information necessary to select a pulse oximeter well suited to your particular needs.

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TECHNICAL COMMUNICATIONS

Selection of Implantable Narcotic Delivery Systems

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WALDMAN SD, COOMBS DW. Selection of implantable narcotic delivery systems. Anesth Analg 1989;68:377–84.

Intraspinal narcotics have dramatically influenced the way pain of malignant origin is managed. There has been a rapid acceptance of this modality within the anesthesia community to treat a wide variety of cancer pain problems. In tandem the development of various implantable narcotic delivery systems has complemented and facilitated the expanded role of intraspinal narcotics in the treatment of cancer pain. Appropriate patient selection is crucial if optimal results are to be achieved. Factors to be considered in patient selection should include the results of the preimplantation spinal narcotic trial, infection and local conditions, hematologic status, physiologic and behavioral abnormalities, cost, patient support systems and life expectancy. By interfacing these factors with the unique profiles that each of the five types of implantable narcotic delivery systems offer, improved results both in terms of pain relief and patient satisfaction can be expected.

Key Words: ANALGESICS—morphine. ANESTHETIC TECHNIQUES—implantable narcotic delivery systems; intraspinal narcotics. PAIN—implantable narcotic delivery systems.

Intraspinal narcotics (ISN) have dramatically influenced the way pain of malignant origin is managed. The continued decline in the number of neurodestructive procedures performed to palliate cancer pain attests to this fact. A vast literature now exists describing ISN use in a variety of clinical situations (1). The principal worries surround the limited data to support the use of ISN to treat non-malignant pain and the increasing use of drugs not approved for use in the epidural and subarachnoid space (2). On the positive side, anesthesiologists have adapted the technique to relieve cancer pain in thousands of patients and, in so doing, have substantially increased the visibility of the specialty in a role as pain specialist in the community at large. In tandem the development of various implantable narcotic delivery systems (INDS) has occurred to complement and facilitate the expanded role of intraspinal narcotics in the palliation of cancer pain (3,4,5).

Table 1 describes the five basic types of INDS. Anesthesiologists are familiar with types one and two (Figs. 1, 2). The Type III system (Fig. 3) consists of a totally implantable injection port that is attached to a Type II tunneled catheter. The Type IV system is a totally implantable mechanically activated pump/reservoir that is attached to a Type II tunneled catheter. An example of this system is shown in Figure 4. The propotype of the Type V system is a totally implantable continuous infusion pump. This is connected to a Type II tunneled catheter (Fig. 5).

The purpose of this communication is to outline the basic factors that need to be considered when selecting an INDS to insure optimal outcome both in terms of pain relief and patient satisfaction.

Considerations Before Implantation

Patient Selection

Appropriate patient selection is crucial if optimal results are to be achieved both in terms of palliation of pain and patient satisfaction. Factors that must be

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Table 1. Intraspinal Narcotic Delivery Systems

Type I	Percutaneous epidural or subarachnoid catheter
Type II	Percutaneous epidural or subarachnoid catheter with subcutaneous tunneling
Type III	Totally implanted epidural or subarachnoid catheter with subcutaneous injection port
Type IV	Totally implanted epidural or subarachnoid catheter with implanted reservoir/bag and manual pump
TYPE V	Totally implanted epidural or subarachnoid catheter with implanted infusion system

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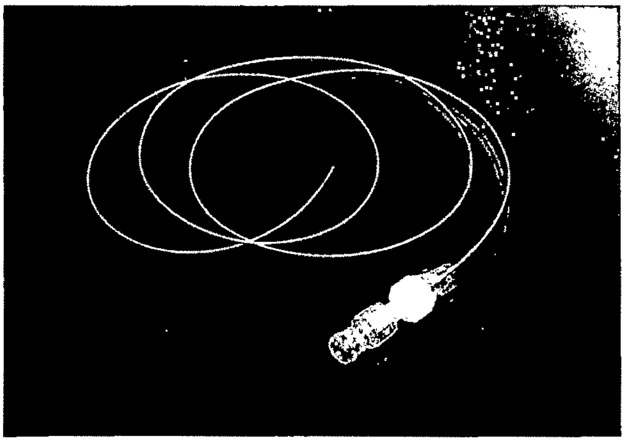

Figure 1. Type I INDS-Percutaneous epidural or subarachnoid catheter.

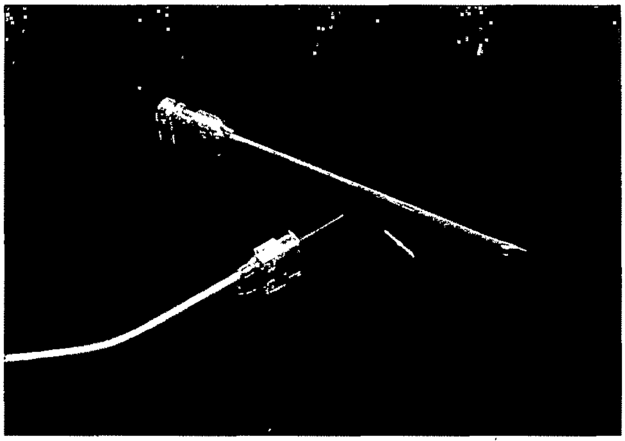

Figure 2. Type II INDS-Tunneled epidural or subarachnoid catheter.

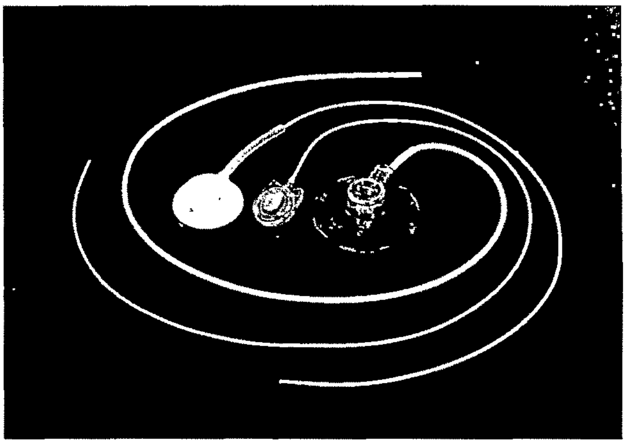

Figure 3. Type III INDS-Totally implanted epidural or subarachnoid catheter with subcutaneous injection port.

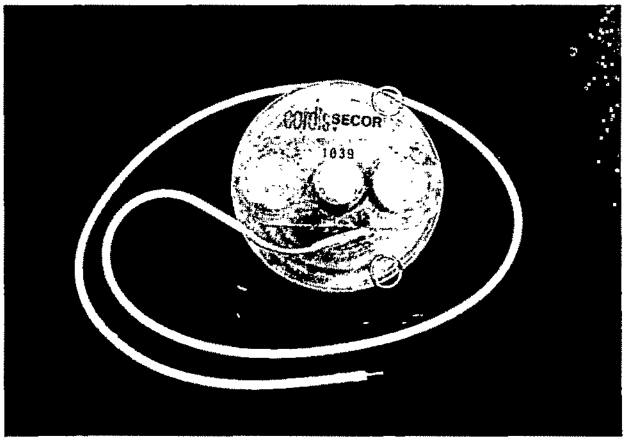

Figure 4. Type IV INDS-Totally implanted epidural or subarachnoid catheter with implanted manually activated pump.

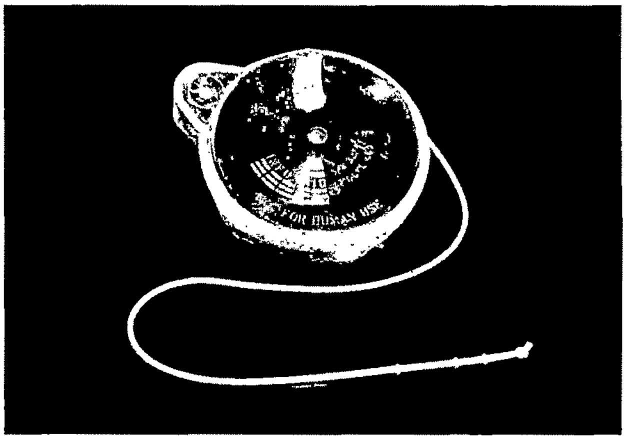

Figure 5. Type V INDS-Totally implanted epidural or subarachnoid catheter with implanted infusion system.

considered prior to placement of an INDS are summarized in Table 2.

Preimplantation Trial

The first responsibility to the cancer pain patient is to make a diagnosis of the pain problem and to analyze the appropriateness of the patient's analgesic prescription. If the diagnosis and therapy are correct, if the extent of disease is defined, and if oncologic and analgesic therapy have been maximized, it is appropriate to proceed to a trial of spinal narcotics.

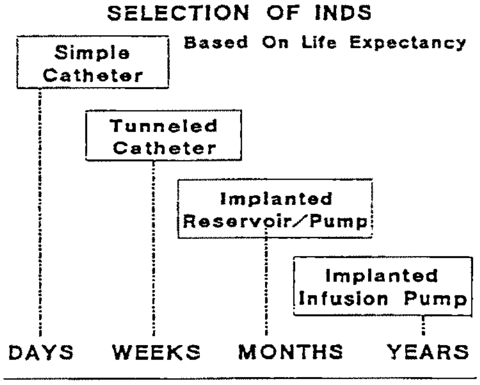

Figure 6. Selection of implantable narcotic delivery systems based on life expectancy.

Table 2. Preimplantation Considerations

1. Results of preimplantation trials of intraspinal narcotics
2. Infection
3. Clotting disorders
4. Behavioral abnormalities
5. Physiologic abnormalities
6. Cost of delivery system
7. Cost of drugs, needles, and supplies
8. Evaluation of support system
9. Concurrent therapy

Table 3. Protocol for Preimplantation Trials of Intraspinal Narcotics

1. Explain procedure, expected goals, and potential side effects to patient and family
2. Select an appropriate narcotic for intraspinal administration.
3. Determine the appropriate dosage and volume of diluent expected to relieve pain.
4. Administer the intraspinal narcotic and diluent via the intended rout of delivery, i.e., epidural or subarachnoid.
5. Quantify on a flow sheet the duration of pain relief, level of activity, amount of sleep, and need for additional narcotic analgesics.
6. Quantify the side effects of intraspinal narcotics.
7. Repeat the trial to quantify the results.
8. Observe for 24 hours after intraspinal narcotics and requantify variables listed in #5 above before proceeding with implantable INDS.

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The next factor to consider when selecting a patient for an INDS is whether intraspinal narcotics adequately relieve the patient's pain. Not all pain is relieved by intraspinal narcotics (6). For this reason, generally an INDS should never be implanted without first verifying the ability of intraspinal narcotics to relieve the patient's pain (7). The magnitude of relief should be greater than 50% of the preinjection intensity with a duration of at least twice the half life of the agent, i.e., 8–12 hours in the case of morphine (5).

Table 3 outlines a suggested protocol for the preimplantation trial of intraspinal narcotics. If a question remains as to the ability of intraspinal narcotics to provide pain relief after two trial doses, a placebo injection may help clarify the situation. Failure to clearly demonstrate the efficacy of intraspinal narcotics during the preimplantation trial could subject the patient to implantation of a delivery system that fails to achieve the desired results—namely, pain relief. Such a failure may occur for several reasons, including test injections that are not made into the correct place, psychological reasons such as depression, advanced tolerance to opioids, incorrect dose of spinal opioids, or because a principal component of the patient's pain syndrome is not susceptible to opioid action, i.e., central pain (4,7). With the exception of electrical stimulation and spinal narcotic analgesia, few invasive pain therapies allow the patient and physician to test the therapy before an irreversible result has occurred. Local anesthetic blocks are useful in educating the patient prior to neurodestructive procedures, but cannot always predict the adequacy, extent, or complications of an irreversible destructive procedure.

Infection and Local Conditions

Infection, inflammation, or dermatitis at the proposed dermal site of implantation or the presence of generalized sepsis obviously represent absolute contraindications to proceeding with implantation. Many cancer patients have infected pressure sores, colostomies or iliostomies, or chronic infections in areas of tumor necrosis. Our experience is that an INDS may be placed if attention to sterile technique is adhered to during implantation, injection, or refill of the INDS. Prophylactic antibiotic use should also be considered during placement of implantable ports and pumps.

Specific issues arise relative to the placement site of the port or pump component of the delivery system. Edema is common among cancer patients and care must be taken when choosing a placement site to avoid dependent areas where an increase in edema may make palpation and injection of a delivery system impossible. Both condition of the skin and subcutaneous tissues as well as the presence of other equipment such as colostomy bags, percutaneous drainage catheters and the like may influence where a delivery system is placed. Inanition may leave little subcutaneous adipose to cushion a prominent port or pump against the trauma of repeated percutaneous needle punctures and may result in breakdown of the skin and subcutaneous tissues surrounding the delivery system. The latter consideration leads the thoughtful physician to carefully evaluate the type and profile (physical contour) of implantable devices, particularly port systems since they will be frequently accessed. Simply put, obese patients require higher profile septums to make location of the injection port more reliable by palpation while thinner patients require lower profile systems and a site with as much subcutaneous adipose tissue as possible.

Multiple ostomies and/or abdominal scars may lead one to choose a subclavian chest wall implant site to facilitate creation of the subcutaneous pocket and later to reduce the risk of bacterial contamination during punctures after the patient has returned home. Finally, both ease of access and the impact of ambulation and position must be considered. Paraprofessionals and family are often charged with performing injections, refills, and wound care. Therefore the location of the system should be selected with their capabilities and limitations in mind. A delivery system that is difficult to palpate may lead to abandonment by the ancillary personnel involved. Implantation of delivery systems too close to rib margins may lead to recurrent costochondral irritation with bending over; similarly, some patients may have difficulty with belts, brassieres, or ostomy bags with poor selection of device or location. It is at times surprising that despite successful control of pain with the implanted delivery system, the patient becomes so annoyed by side effects of placement that much of the success is nullified.

Anticoagulation and Hematologic Abnormalities

The fully anticoagulated patient represents a special problem when considering placement of an INDS. Preimplantation trials of intraspinal narcotics for relief of pelvic and lower body pain has been carried out in the presence of anticoagulation by administering the proposed narcotic caudally utilizing a 25 gauge × 1.6 cm needle (8). Intraspinal narcotics administered in the lumbar or caudal region may not relieve upper body pain of malignant origin without substantial and unnecessary increase in doses of opioids injected. One must carefully weigh the risk/benefit ratio of stopping anticoagulants in order to proceed with preimplantation trials of cervical or thoracic ISN.

Coagulopathy is frequently observed in patients either due to chemotherapy or the tumor itself, i.e., fibrinolysis with prostatic cancer. Platelet count and function, and tests for procoagulant factor activity should be assessed if the history or physical examination suggest a significant preoperative coagulopathy.

Table 4. Common Physiologic Abnormalities that May Interfere with the Patient's Ability to Assess Pain Relief

- Metabolic encephalopathy
  - Hypercalcemia
  - Hyponatremia
  - Hypoxemia
  - Hypercarbia
  - Azotemia
  - Hepatic encephalopathy
  - Paraneoplastic syndrome
- Drug-induced organic brain syndrome
  - Narcotic
  - Minor tranquilizers
  - Barbiturates
  - Phenothiazine reactions
  - Cimetidine
- Structural brain disease
  - Metastatic tumor
  - Increased intracranial pressure
  - Pre-existing structural abnormalities
  - Cerebral infarction
  - Cerebral hemorrhage
  - Abscess
- Pre-existing neurodegenerative disorders
  - Alzheimer's disease

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Physiologic Abnormalities

Physiologic abnormalities may impair the patient's ability to assess the adequacy of pain relief (Table 4). Many abnormalities are reversible and an effort should be made to correct them before a trial of intraspinal narcotics is undertaken. It should be remembered that central nervous system abnormalities may be incorrectly interpreted as uncontrolled pain by the patient and pain management specialist alike (9).

Behavior Abnormalities

Behavioral abnormalities may affect the patient's ability to assess the adequacy of pain relief and are often difficult to identify (Table 5) (7,10). These issues may coexist with physiologic factors, but care must be taken not to attribute inadequate pain relief solely to behavioral factors until all other factors have been explored.

Cost

The cost of both the intended delivery system and the drugs to be administered through the delivery system

Table 5. Common Behavioral Abnormalities that may Interfere with the Cancer Patient's Ability to Assess Cancer Pain

1. Pre-existing psychiatric disroder, e.g., depression
2. Pre-existing chemical dependence
3. Use of pain as an attention seeking device
4. Use of pain to obtain more medication to alter the sensorium
5. Patient's refusal to accept the person designated as care-giver
6. Patient's use of pain to punish certain care-givers

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must be considered prior to implantation of an INDS. A perfectly functioning INDS is of no value to the patient who is unable to pay for the narcotics, special needles, and supplies needed to use the delivery system. Similarly, implanted systems may superimpose financial hardship upon a difficult terminal course. With prior planning, the financial issues can be individualized and financial tragedy averted.

Support System

An INDS requires a baseline level of commitment not only from the patient but from the support system as well. The person or persons designated as the patient's support system must be acceptable to the patient in the role of care provider. If this is not the case, problems may arise. This person must be available all day and night to care for and inject the INDS should the patient be unable to do so. It should be remembered that the patient who injects his own INDS initially may be unable to do so later in the course of his disease. This inability or unwillingness of the support system to care for and inject the INDS has significant implications when selecting the appropriate INDS (see below).

Life Expectancy

Prediction of a cancer patient's life expectancy can be difficult. However, an estimate in terms of days, weeks or months is essential to aid the selection of an appropriate INDS (Fig. 1). Often the patient's general condition will improve if adequate pain control is provided either because of reduced anorexia, relief of constipation, or better overall psychological state. This must be taken into account when estimating life expectancy.

Type of INDS

There are essentially five types of INDS (Table 1) (3,7). Each has its own profile of advantages and disadvantages. Understanding these unique qualities of each INDS allows for more intelligent selection.

Type I Percutaneous Catheter

The percutaneous catheter has three applications in cancer pain management. The first is in the acute setting for the delivery of narcotics into the epidural or subarachnoid space in order to provide temporary palliation of pain postoperatively or until other concurrent treatments become effective to relieve the patient's pain, e.g., radiation therapy, chemotherapy, surgery, etc. The second application is in terminally failing patients too ill for more invasive procedures (11,12). A third application is the use of a percutaneous catheter to administer test doses of intraspinal narcotics prior to placement of a more permanent INDS.

The advantages of a percutaneous catheter include:

1. Ease of placement at the bedside without need for special instruments.
2. Minimal sedation or local anesthesia required.
3. Low cost relative to other delivery systems.
4. Can be (re)placed on an outpatient basis.
5. Can be attached to an external continuous infusion pump.

The disadvantages include:

1. Risk of infection with long term use.
2. Kinking, leakage, breakage, or displacement of the catheter.
3. Fibrosis around the catheter leading to decreased narcotic efficacy or pain on injection.

In many centers, the use of a percutaneous catheter for the delivery of epidural and especially subarachnoid narcotics is somewhat limited. Improved catheter fixation and reduced risk of infection associated with tunneling and relative ease of the tunneling (13,14), have led many pain specialists to tunnel the intraspinal catheter to the flank, abdomen, or chest wall.

Type II Subcutaneous Tunneled Catheters

Subcutaneously tunneled catheters are usually selected for cancer patients with life expectancies of weeks to months who also have experienced excellent palliation of pain with trial doses of intraspinal narcotics.

The advantages of this type of delivery system consist of:

1. Ease and low cost of implantation.
2. Potentially less risk of infection compared with percutaneous catheters.
3. Simplified catheter care.
4. Ease of injection by both medical and non-medical personnel.
5. Ease of removal or replacement.
6. Outpatient implantation feasible.
7. Can be attached to an external continuous infusion pump.

The disadvantages include:

1. Possible kinking, obstruction and dislodgement of catheter.
2. External portion of the catheter susceptible to breakage.
3. Pain on injection and/or fibrosis about the catheter still occurs.

Type III Totally Implantable Reservoir/Port

The totally implantable reservoir is often chosen for use in cancer patients with life expectancies measured in months to years who have had excellent relief of pain with trial doses of intraspinal narcotics (15).

The advantages of this system are:

1. Potentially less risk of infection than with Type I and II systems.
2. Decreased risk of catheter failure.
3. Inadvertent displacement unlikely.
4. Outpatient placement feasible.
5. Subarachnoid delivery more feasible than with Type I and Type II systems.
6. Both bolus and continuous delivery possible (external pump).

The disadvantages are:

1. Injection often more difficult than with Type I and II systems.
2. Skin puncture pain with each delivery system use.
3. Increased cost of delivery system.
4. Special needles may be required that can add significantly to cost.
5. Continuous delivery mode requires inconvenience of an external pump but bolus injections may have side effects that continuous infusion techniques do not have.
6. Removal or replacement requires a surgical incision.

Type IV Totally Implantable Reservoir/Bag and Mechanically Activated Pump

Poletti and colleagues created one of the earliest totally implantable systems for patient activated drug delivery (16). This system consisted of an implantable sterile blood bag with a hydrocephalus shunt valve in series with the bag and intraspinal catheter. The valve could be activated by the patient to allow narcotic self-administration from the implanted bag. This concept has now been extended by Cordis, through introduction of a totally implantable reservoir that is accessed percutaneously through a septum on the surface of the device. However, the device also has a mechanical valve system activated by a set of buttons on the pump surface. The patient can deliver spinal narcotic if the buttons are depressed in the proper sequence (17).

The advantages of the Type IV system include:

1. Potentially less risk of infection than with Type I, II and III systems.
2. Fewer skin punctures than with type III system.
3. Decreased risk of catheter failure.
4. Inadvertent displacement unlikely.
5. Subarachnoid delivery more feasible than with Type I and II systems.

The disadvantages include:

1. Injection is more difficult than with Type I and II systems.
2. Only bolus mode possible and, thus, inadvertant or intentional patient overdosage is possible.
3. Greater cost than with Type I, II and III systems but less than with Type V systems.
4. Special needles required that can add significantly to cost (true also of most III, IV, and V systems).
5. Outpatient placement not feasible.
6. Removal or replacement requires a surgical incision.

Type V Totally Implantable Infusion Pump

The totally implantable infusion pump is also used in cancer patients with life expectancies measured in months to years and in whom relief of pain was observed after trial doses of intraspinal narcotics (18). Type V delivery systems may also be indicated in a cancer patient with a shorter life expectancy. Such situations arise in patients in whom intermittent confusion occurs secondary to metabolic or physiologic abnormalities or in patients (often aged) prone to narcotic-induced confusion. Repeated bolus injection of spinal narcotics often leads to recrudescence of the same CNS complications that can be seen with sustained release or extended duration systemic narcotics such as methadone. A low dose continuous intraspinal narcotic infusion may obviate this problem while providing convenient and effective analgesia. Alternatively, an implanted port with an externally functioning infusion pump may suffice albeit with at times substantial inconvenience and increased ancillary support requirements. Since these systems require infrequent refills and run continuously, they are ideal for patients with limited medical or nonmedical family support services. The overall cost is however a prohibitive factor that may result in selection of at times less effective or at least more inconvenient analgesia.

Totally implanted infusion reservoirs can be further subdivided into two subtypes: 1) Continuous infusion systems with or without auxiliary injection ports, and 2) programmable infusion pumps (4,19). To date the majority of experience is with continuous infusion reservoirs. The latter are usually selected with an auxiliary injection system to take advantage of the potential options, i.e., local anesthetic injections, etc., available with this additional system (See below). Further, the cost of these systems is to date substantially less than programmable systems. Programmable systems are implanted with the same ease and allow a broad spectrum of delivery rates and modes, including occasional bolus injections. Their principal application to date has been tied to intrathecal infusion and especially the therapy of spasticity in multiple sclerosis and spinal cord injured patients. There is yet no proven advantage of programmable systems over the simpler continuous infusion systems, despite theoretical advantages, in cancer pain patients.

Advantages of the type V system are:

1. Minimal risk of infection after perioperative period.
2. Frequent injections eliminated (pump reservoir needs to be refilled approximately once every 7–20 days).
3. Potentially decreased risk of the development of tolerance.
4. Possibly less risk of confusion or respiratory depression.
5. Occasional bolus injections feasible (auxiliary port models only or programmable systems).
6. Intrathecal or epidural delivery feasible.

The disadvantages are:

1. Expensive.
2. Heavy IV sedation with local anesthesia/regional anesthesia or/general anesthesia required for implantation.
3. Outpatient placement may be less feasible.
4. Fixed delivery rate offers less flexibility as tolerance develops (nonprogrammable system).
5. Combined narcotic/local anesthetic currently not practical.
6. Revision or replacement requires surgical incision.
7. Maximum dose a factor of agent solubility and absolute flow rate.

Choice of Epidural or Subarachnoid Catheterization

There are advantages and disadvantages to both epidural and subarachnoid catheterization for delivery of intraspinal narcotics. In some instances, the catheter terminus does not have a significant impact, for example, radiographic contrast may be administered either epidurally or in the subarachnoid space to confirm catheter location or assess the progression of spinal metastatic disease.

The advantages of epidural catheterization include:

1. Placement feasible at any dermatomal level.
2. No risk of spinal fluid leakage or related spinal headaches.
3. Should infection develop it will be limited initially to the reservoir pocket, catheter tunnel providing time for treatment before it reaches the epidural space.
4. Lower peak spinal fluid levels during bolus injections.
5. Lower incidence of respiratory depression with bolus injections.

The disadvantages of epidural catheterization include:

1. Epidural fibrosis around catheters with subsequent decrease in efficacy or pain on injection.
2. Inability to deliver opioid peptides to the central nervous system due to their low lipid solubility (a future issue).

The advantages of subarachnoid catheterization include:

1. No dural reaction or fibrosis surrounding catheter.
2. Lower initial drug doses required.
3. Lower incidence of systemic side effects.
4. Spinal fluid sampling possible for culture, diagnosis or drug levels.
5. Peptide administration feasible.
6. Administration of intrathecal antibiotics and chemotherapy possible.

The disadvantages of subarachnoid catheterization include:

1. Infection would produce an early meningitis.
2. Spinal headaches, if persistent, may require surgical closure of the spinal fluid leak.
3. The development of subcutaneous spinal fluid hygromas may have several consequences:
   a) make difficult refilling or injection of ports or implanted infusion pumps.
   b) narcotic dilution occurs with reduced analgesic efficacy;
   c) if wound breakdown occurs a CSF cutaneous fistula may develop.
4. CSF leaks may lead to intracranial subdural hematoma due to tearing of subdural veins.

Implantable narcotic delivery systems are useful adjuncts to cancer pain management. Proper selection of both patients and appropriate delivery systems is crucial if optimal results are to be achieved. It should be recognized that the chronic administration of opioids and other drugs into the epidural or subarachnoid space is in its infancy. Advances in the pharmacology of spinal drugs and the development of new delivery system technology will in time no doubt expand the options available for the relief of cancer pain (4).

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Phonocardiography as a Monitor of Cardiac Performance During Anesthesia

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HANSEN PB, MILETICH DJ, ALBRECHT RF. Phonocardiography as a monitor of cardiac performance during anesthesia. Anesth Analg 1989;68:385–7.

The usefulness of phonocardiography as a monitor of cardiac performance during anesthesia was investigated in six dogs. Anesthetic depression by halothane, isoflurane and nitrous oxide was demonstrated by the phonocardiogram. Likewise, the stimulating effect of dopamine clearly showed in the recordings. Changes in the amplitude of the first heart sound were found to correlate closely with changes in the maximum rate of rise of left ventricular pressure ($r = 0.9551$, $P < 0.001$). Simultaneous changes in cardiac output and arterial pressure also occurred.

Cardiac depression from anesthetics and/or disease is a major concern during anesthesia. Perioperative phonocardiography, a simple and noninvasive procedure, merits further investigation as a possible monitor of cardiac performance.

Key Words: MEASUREMENT TECHNIQUES, phonocardiography. HEART, phonocardiography.

Use of a precordial or esophageal stethoscope to monitor breath and heart sounds is standard anesthesiological practice. Attempts to obtain quantitative information from the heart sounds during anesthesia, however, have been few.

Traditionally, the first heart sound is explained by the forceful closure of the mitral valve (1). More recent studies show that the first heart sound is created by accelerations and decelerations of blood within the heart and great vessels, thus linking the first heart sound to the force of cardiac contraction (2). In fact, changes in the amplitude of the first heart sound (S_1) and the maximum rate of rise of left ventricular pressure (dP/dt) have been found to correlate in a variety of experimental situations (3).

Because cardiac depression from anesthetics and/or disease is a major perioperative concern, we have tried to determine if monitoring S_1 might provide information about cardiac performance during anesthesia.

Materials and Methods

Six adult mongrel dogs of either sex weighing 25–35 kg apiece were used in this study following protocol approval by the Michael Reese Animal Care Committee. The dogs were surgically prepared at least 8 days prior to study. Preparation included implantation of central venous and aortic catheters, placement of an electromagnetic flow probe on the pulmonary artery and a #7F balloon tipped catheter in the left ventricle inserted through the left atrium. Catheters and leads were tunneled subcutaneously and externalized on the back. A tracheostomy was performed in order to avoid deep general anesthesia needed for orotracheal intubation during the study.

Phonocardiograms were obtained using an HP-21050-A contact microphone strapped to the chest wall at the point of maximal stethoscopic loudness of S_1. The signal was recorded through an HP-8813-A sound amplifier with a high pass filter at 50 Hz and a slope of 24 dB/octave. Microphone position and gain settings were kept constant during each study. The amplitude of S_1 was obtained in mm from the recording paper; this value can be converted to dB by a calibration signal in the sound amplifier.

Arterial, venous and left ventricular pressures were measured in mm Hg by HP-1280-C transducers

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and HP-8805-C/D amplifiers calibrated to zero at mid chest level.

The dP/dt was measured in mm Hg/sec by a HP-8814-A derivative computer with a low pass filter at 50 Hz. The use of fluid filled catheters for recording dP/dt is not recommended for precise measurements (4). However, because only relative changes of dP/dt within each investigational period were considered, the possible error is minimal.

Cardiac output was determined in l/min with the flow probe connected to a Statham SP-2202 blood flowmeter. Lead II of the ECG was obtained.

All data were recorded on a HP-7758 recorder at a paper speed of 50 mm/sec. Measurements were obtained on a beat to beat basis and averaged over a full respiratory cycle. For each animal, changes in parameters were expressed as percentage change from baseline value (Δ%) within each experimental period. Statistical evaluations were made using paired *t*-test and least square linear regression analysis. Results are expressed as mean ± SEM.

After sedation with midazolam (0.1 mg/kg) and fentanyl (0.02 mg/kg) the animals were placed on an operating table in the left lateral decubitus position. An infusion of normal saline 5 ml·kg^{-1}·h^{-1} was started. The tracheostomy was intubated and 100% O_2 delivered through a circle anesthesia system with CO_2-absorber using a fresh gas flow of 4 l/min. Etomidate (0.2 mg/kg) and vecuronium (0.1 mg/kg) was administered and positive pressure ventilation delivered at a rate of 12 breaths per min with a tidal volume of 12 ml/kg. Monitoring equipment was attached, and after 10 min of stable circulation values, baseline recordings were obtained.

Each animal was studied using the following three protocols on three different occasions separated by at least 2 days: 1) Halothane was administered in increasing doses of 0.7, 1.0, 1.5 and 2.0%. Each concentration was maintained for 30 min before recordings were made. During stable 1.0% halothane anesthesia 50% N_2O was added to the inhaled gas for 15 min with recordings obtained during pure 1.0% halothane anesthesia for 15 minutes and recordings made before, during and after addition of N_2O. The mean value of the two recordings obtained during pure 1.0% halothane anesthesia was used as baseline for the evaluation of N_2O effect. 2) Halothane was replaced by isoflurane in 1.0, 1.5 and 2.0% inspired concentration. The effect of adding 50% N_2O was investigated during 1.5% isoflurane anesthesia. 3) During stable 1.5% isoflurane anesthesia, dopamine was infused in increasing doses of 2.5, 5.0 and 10.0 μg·kg·/min^{-1}. Recordings obtained during 1.5% isoflurane anesthesia were used as baseline for the evaluation of dopamine effects. Dopamine was infused in non-randomized order, each dosage added on top of the preceding. Each dosage level was maintained for 15 minutes before recordings were made.

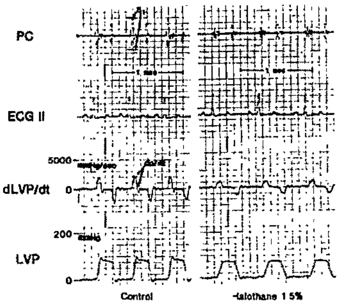

Figure 1. Example of baseline tracings (control) and tracings obtained during 1.5% halothane anesthesia in one dog. Phonocardiogram (PC), ECG lead II, first derivative of left ventricular pressure (dLVP/dt) and left ventricular pressure (LVP) represented. Note the reduction in the amplitude of the first heart sound (S_1) and the maximum rate of rise of left ventricular pressure (dP/dt) induced by halothane.

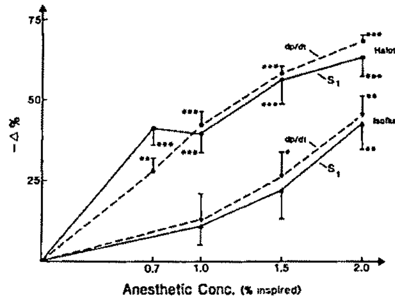

Figure 2. Dose-response relationship between percent decrease from baseline values (−Δ%) in S_1 (solid line) and dP/dt (broken line) induced by increasing concentrations of halothane or isoflurane. Mean and SEM values indicated. *Significantly different from control value *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Results

An example of tracings obtained before and during 1.5% halothane anesthesia is given in Figure 1. Note the marked reduction of the amplitude of S_1 in the phonocardiogram induced by halothane.

Figure 2 shows the depressant of halothane and isoflurane on S_1 and dP/dt. A clear dose-response relationship is evident with respect to both S_1 and dP/dt for both anesthetics.

Addition of 50% N_2O to a stable 1.0% halothane anesthesia induced significant reductions in both S_1 and dP/dt (7.7 ± 2.7% and 10.0 ± 3.9%, respectively; $P < 0.05$) below levels seen with halothane alone. During 1.5% isoflurane anesthesia N_2O significantly reduced dP/dt (9.5 ± 3.4%, $P < 0.05$) compared to isoflurane alone, whereas S_1 did not change (0.8 ± 7.2%).

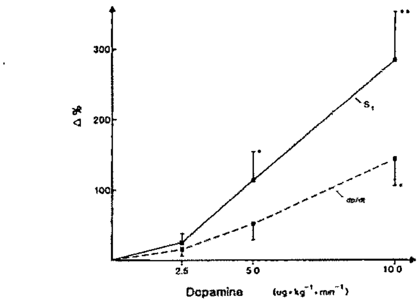

Figure 3. Dose-response relationship between percent increase above baseline values (Δ%) in S_1 (solid line) and dP/dt (broken line) induced by infusion of dopamine in increasing doses during 1.5% isoflurane anesthesia. Mean and SEM values indicated. *Significantly different from baseline values $P < 0.05$, **$P < 0.01$.

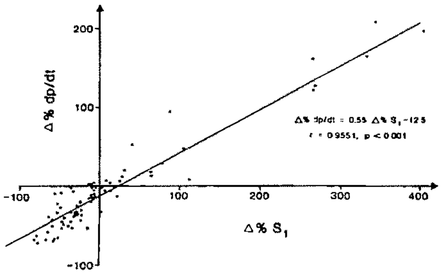

Figure 4. Linear correlation between percent change from baseline values (Δ%) in S_1 and dP/dt. All measured values throughout all investigational periods included in analysis. Total number of data pairs is 72.

Figure 3 shows the effects of dopamine infusion on S_1 and dP/dt during 1.5% isoflurane anesthesia. Both S_1 and dP/dt increased in a dose dependent fashion above values obtained with isoflurane alone. The correlation between changes in S_1 and dP/dt is depicted in Figure 4. Values from all animals in all study periods are included. A strong positive linear correlation was found with $r = 0.955$ (total $n = 72$, $P < 0.001$). The squared correlation coefficients (r^2) between changes in S_1 and changes in dP/dt, cardiac output, mean arterial pressure and heart rate were 0.91, 0.58, 0.27, and 0.007, respectively. The correlations were all significant at $P < 0.05$ except the correlation with heart rate.

Discussion

Early studies have shown changes in S_1 during anesthesia (5–7). It was suggested that these changes reflected cardiac depression (5,6), or changes in volume, of blood within the heart (8). The analyses used in these studies were often semi-quantitative. A more recent study processed the phonocardiograms by a Fourier analysis and linked changes in S_1 to changes of other non-invasively obtained data (9).

This study demonstrates that the raw data from a standard phonocardiographic tracing can be used without elaborate analysis. Both the depression caused by anesthetics and the positive inotropic action of dopamine were clearly demonstrable. A strong positive correlation between changes in S_1 and dP/dt was observed. The N_2O failed to change S_1 as opposed to a reduction in dP/dt during isoflurane; this was probably due to random error since the SEM of S_1 was large.

With proper automation, an online digital readout of S_1 (expressed either in dB or as a percentage of a pre-anesthetic control level) could be developed. This device could give the anesthetist information on cardiac performance on a beat-to-beat basis. However, multiple practical and theoretical problems need investigation before such a monitor can be developed or recommended. Transmission of operating room noise, movement of dressings and dislocation of the microphone can be minimized by using an esophageal microphone. Changes in heart rate as well as pre- and after load affect dP/dt (4) and may influence S_1 (3). Changes in cardiac rhythm represent a special problem since changes of the P-R interval profoundly affect S_1 (1). In this study it appears as if S_1 is more closely related to dP/dt during myocardial depression by halothane or isoflurane (Fig. 2) than during stimulation with dopamine (Fig. 3). This may be related to dopamine induced changes in heart rate or P-R interval, but our data do not justify a detailed analysis.

Despite these questions, we believe that monitoring of S_1, which is simple and noninvasive, could be of benefit in monitoring cardiac performance during anesthesia.

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Clinical Reports

Isoflurane in Obstetrics

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Key Words: ANESTHESIA, OBSTETRIC: isoflurane
ANESTHESIA, VOLATILE: isoflurane

The use of subanesthetic concentrations of inhalation anesthetics for relief of pain during labor and delivery offers advantages to the mother and the newborn during vaginal delivery. In patients requiring pain relief in whom regional anesthesia is either not possible or not desired, inhalation analgesia offers a safe and effective alternative. It provides rapid pain relief and does not impair upper airway reflexes while the mother remains awake enough to participate actively in the delivery. Furthermore, there is no decrease in uterine contractility (1) and no depression of the newborn (2–8).

Isoflurane, a relatively new agent that has low blood: gas solubility and produces anesthesia rapidly, has been extensively studied in animals and surgical patients but its use in obstetrics has not been adequately evaluated.

We investigated the use of isoflurane in subanesthetic doses for analgesia during the second stage of labor in normal vaginal deliveries.

Methods

After approval from the Committee on Human Research and informed consent were obtained, 60 healthy parturients undergoing normal vaginal delivery were randomly assigned to one of two groups: group I (n = 30) received isoflurane 0.2–0.7% (inspired) in oxygen; and group II (n = 30) received nitrous oxide, 30–60%, in oxygen.

An anesthesiologist administered the analgesic mixture continuously. The inhalation analgesic was initiated in the delivery room during the second stage of labor to relieve pain. We adjusted the concentration of each agent to provide optimal analgesia while keeping the patient awake, cooperative, and oriented. The usual inspired concentration of isoflurane needed was 0.4% and for nitrous oxide 33%. The anesthetic circuit used for the administration of the inhalation analgesic was a circle absorber system. Neither patient nor obstetrician was aware of which was being administered. At the moment of birth, the administration of the analgesic mixture was discontinued, and the mother's attention was directed toward her infant.

In each case, the patient, anesthesiologist, and obstetrician assessed the quality of analgesia (Table 1) by ranking it on a scale of 0 (no relief) to 4+ (excellent pain relief). Shortly after delivery, patients were asked if they would be willing to receive the same agent at a future delivery, and whether they remembered the birth of their baby. Blood loss during delivery was estimated by the obstetrician.

Neonates were evaluated by Apgar Scores at 1 and 5 minutes, by cord acid base status and by the Neurologic and Adaptive Capacity Scores (NACS) at 15 minutes, 2 hours and 24 hours of age (9).

Apgar scores were determined by a pediatrician unaware of which drug had been administered to the mother. NACS was performed by a research fellow also unaware of the drug given to the mother.

Maternal blood was analyzed for levels of hemoglobin, hematocrit, biochemical profile and fluoride ion concentration before administration of analgesia and 12 to 24 hours postpartum. At these times, urine specimens were also obtained to determine osmolality and sodium, potassium and fluoride ion concentrations. The newborn's first voided urine was analyzed for osmolality and sodium, potassium and fluoride ion concentrations. Data were analyzed for

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Table 1. Criteria for Scoring Degree of Analgesia for Birth of Baby

Analgesia Score	Parturient	Physician
4+	"Absolutely no pain"	Excellent, no observable signs of pain
3+	"Very little pain"	Very good, slight grimace
2+	"Definitely helped" or "not bad"	Fair, some movement or complaint at height of contraction
1+	"Hardly any relief"	Poor, little apparent relief
0	"None or worse"	None, no demonstrable analgesia

statistical significance using Student's *t*-test or chi-square when appropriate. A P value of <0.05 was considered statistically significant.

Results

Assessment of the Parturient

Both groups of parturients were similar in age, height, weight, parity and infant gestational age and weight with the unimportant exception of the maternal age which was slightly higher in group II patients. Both groups were also similar in type of local anesthetic technique used for delivery (Table 2).

More than 83% of parturients in both groups had spontaneous vaginal deliveries; the rest were delivered by forceps. The duration of prepartum inhalation analgesia was similar in both groups (Table 2). There were no anesthetic complications. Analgesia was considered satisfactory if a score of 3+ or 4+ was given. Isoflurane and nitrous oxide were given similarly high scores by mothers, anesthesiologists and obstetricians. No patients in either group had amnesia except for one patient given isoflurane who had difficult forceps delivery and was given 20 mg of ketamine and had partial amnesia. No significant differences existed between the two groups regarding either patient satisfaction with the technique or blood loss as estimated both by the obstetrician and by evaluation of hemoglobin and hematocrit values before and after delivery.

Assessment of the Neonate

All neonates were vigorous at 5 minutes and the incidence of low 1-minute Apgar scores did not differ significantly between the two groups. Umbilical vein and artery acid base and blood gas data were equally good in the two groups (Table 3).

There were no significant differences between the two groups in test scores for any test item on the NACS. The percentage of infants who scored 35–40 on the NACS was not significantly different in the two groups.

Biochemical Data

Serum electrolyte levels and renal function in the mother, as assessed by determination of serum BUN and uric acid concentrations as well as by urine osmolality and sodium and potassium concentrations, were not significantly different between the two groups Urine osmolality and sodium and potassium concentrations in the newborns were also not significantly different.

Fluoride levels are presented in Table 4. Mean serum fluoride concentrations in mothers 12 to 24 hours postpartum were less than 5.6 μMol/L following N_2O or isoflurane. These values were not significantly different from the preanesthetic levels. In patients who were given isoflurane, urine fluoride concentrations 12 to 24 hours postpartum were higher than in the N_2O group but did not differ significantly from preanesthetic levels.

Discussion

Various inhalation anesthetics, including nitrous oxide (2–6), methoxyflurane (4–7), trichloroethylene (7,8), chloroform (3), cyclopropane (2) and enflurane (10) have been used successfully for inhalation analgesia.

Nitrous oxide, the most commonly used, must be used in concentrations of 30% to 50% to provide adequate analgesia for labor and delivery. This does not permit the delivery of high concentrations of oxygen to the mother, a practice that may be desirable if fetal distress occurs. Although methoxyflurane has been widely used because of its low vapor pressure and high solubility in blood, the onset of analgesia is relatively slow. Also, patients often object to its pungent odor. Trichloroethylene cannot be administered through a CO_2 absorber, and, although popular in England, is no longer commercially available in the United States. Cyclopropane, although possessing excellent analgesic properties, is explosive even in subanesthetic concentrations.

In our study, both isoflurane and nitrous oxide analgesia satisfied patients, anesthesiologists, and

Table 2. Comparative Effects of Isoflurane and Nitrous Oxide Analgesia

	Isoflurane: O_2 (n = 30)	Nitrous Oxide: O_2 (n = 30)
Mean (±SE) Duration of Prepartum analgesia (min)	13 ± 2.4	14.7 ± 2.2
Satisfactory (3+ & 4+) analgesia scores (%):		
Mother	83	87
Anesthesiologist	90	97
Obstetrician	87	83
Amnesia for delivery (%)		
None	97	100
Partial	3	0
Patient acceptance (would pt. have the same agent again?)(%)		
Yes	93	93
No	7	7
Local Anesthetic for Delivery (%)		
None	47	53
Local infiltration	0	3
Pudendal nerve block	20	27
Epidural	7	7
Epidural and pudendal	26	10
Blood Loss		
Mean (±SE) estimated blood loss (ml)	320 ± 24	350 ± 22
Antepartum hemoglobin (g/100 ml)	13.2 ± 0.2	12.7 ± 0.2
12–24 hr postpartum	11.6 ± 0.2	11.0 ± 0.3
Antepartum hematocrit (%)	39.3 ± 0.7	38.2 ± 0.6
12–24 hr postpartum	35.1 ± 0.7	33.1 ± 0.8

No Significant Differences Between Groups

Table 3. Comparison of Newborns Receiving Isoflurane or Nitrous Oxide Analgesia

Apgar Scores	Isoflurane: O_2 (n = 30)	Nitrous Oxide: O_2 (n = 30)
At 1 min (%)		
0–4	0	0
5–7	7	7
8–10	93	93
At 5 min (%)		
0–4	0	0
5–7	0	0
8–10	100	100
Blood Gases		
Umbilical Vein		
pH	7.34 ± 0.01*	7.33 ± 0.01
PCO_2(mmHg)	41 ± 1.3	42.4 ± 1.2
Base Excess (mEq/L)	−3 ± 0.3	−2.8 ± 0.4
PO_2 (mmHg)	33 ± 1.4	32.1 ± 1.4
% oxygen sat.	58 ± 2.9	55.7 ± 2.4
Umbilical Artery		
pH	7.28 ± 0.01	7.27 ± 0.01
PCO_2(mmHg)	50 ± 1.9	51.5 ± 1.5
Base Excess (mEq/L)	−3 ± 0.5	−2.2 ± 0.5
PO_2 (mmHg)	20 ± 0.9	20.1 ± 1.1
% oxygen sat.	26 ± 2.4	26.1 ± 2.2

No Significant Differences Between Groups.
*Means ± SE.

obstetricians. Maternal amnesia was rare and patient acceptance was high. No difference in blood loss with the two agents was detectable.

Table 4. Fluoride Levels with Isoflurane and with Nitrous Oxide Analgesia*

	Isoflurane: O_2 (n = 30)	Nitrous Oxide: O_2 (n = 30)
	(μMoles/L)	
Serum		
Maternal		
Before anesthesia	<5.5	<5.6
12–24 hr. postpartum	<5.6	<5.6
Urine		
Maternal		
Before anesthesia	41.4 ± 4.6	38.9 ± 5.8
12–24 hr postpartum	36.5 ± 3.1**	23.62 ± 2.2
Newborn (first voided urine)	<5.6	<5.6

*Mean ± SE.
**$P < 0.05$ compared to nitrous oxide.

In vitro studies of human uterine muscle indicate that isoflurane at 0.5 MAC produces minimal decreases in uterine contractility, which is similar to that of halothane (11). Similarly, when used in cesarean sections, 0.75% isoflurane does not increase uterine relaxation or bleeding (12). Neonatal outcome was equally good in both groups as determined by Apgar Scores, cord acid base status and the neurobehavioral assessments. There were no biochemical changes indicating maternal or fetal renal disfunction. Maternal serum and urine fluoride ions did not increase significantly after exposure to isoflurane, similarly, newborn urine fluoride concentrations were very low and similar to those in the nitrous oxide group.

We conclude that isoflurane in subanesthetic doses, combined with oxygen, is a safe and effective inhalation analgesic agent for normal vaginal deliveries. Newborns were vigorous, and no biochemical evidence of renal toxicity was detectable in either the parturients or their newborns. Isoflurane has the advantage of permitting delivery of almost 100% oxygen, which may be advantageous if complications occur.

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Evaluation of Five Metallic Tapes for Protection of Endotracheal Tubes during CO_2 Laser Surgery

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Key Words: ANESTHETIC TECHNIQUES, LASER—fires. SURGERY, LASER—fires.

In a survey of CO_2 laser laryngoscopic surgery, Fried (1) observed fires and explosions involving the endotracheal tubes to be the most frequent complications. To prevent this potential catastrophe, the wrapping of combustible endotracheal tubes with metal tape has been recommended (2). However some tapes may not afford adequate protection (3). We sought to evaluate the protection offered by five commercially available metal tapes under extreme conditions of laser energy to see whether a safe technique for clinical use could be established.

Methods

Polyvinylchloride endotracheal tubes (Mallinckrodt Hi-Lo®), 8.0 mm internal diameter (ID), were wrapped with a continuous strip of 1/4 inch (0.6 cm) self-adhesive foil tape. Starting at the distal (cuffed) end, the tube was wrapped in a spiral fashion. The tape was applied in an overlapping manner so that bending of the tube would not expose any unprotected areas. The tapes used were: 3M (St. Paul, MN) nos. 425 (4,5), 1430, and 433, Radio Shack (Tandy Corporation, Ft. Worth, TX) no. 44-1155 (6), and copper foil tape (1-mm thickness) (Venture Tape Corporation, Rockland, MA). During the trials, 5 liters/minute of 100% oxygen flowed through the tubes being tested. We used a Laser Sonics model LS880 CO_2 laser and Zeiss operating microscope, employing a 400-mm lens and 0.68-mm beam diameter. The beam was directed onto the foil-wrapped tubes perpendicularly at the point of overlapping of the tape. A power of 70 watts in the continuous mode of laser operation was used. The time until the appearance of smoke, flames, perforation, or "blow torch" ignition were recorded. Finally, a segment of tape was wrapped adhesive side outward and the procedure repeated to determine whether unexpected contact of the laser with the adhesive would cause combustion.

Results

The 3M tape nos. 425 and 433 and the copper tape were unaffected by 25 seconds of laser impact and thus protect the endotracheal tubes. Endotracheal tube penetration and a blow torch fire occurred at 7 and 14 seconds, respectively, with the Radio Shack and 3M no. 1430 tapes (Fig. 1).

On directing the laser to the reverse side of the tapes, the adhesive backings of the 3M tape no. 433 and the Radio Shack tape were ignited and the tapes perforated within 0.1 second of the laser's impact. Flaming of the adhesive occurred at 1 second without penetration of the 3M tape no. 1430 or the copper tape. The adhesive of the 3M tape no. 425 started to smoke at 2 seconds, but no flames occurred and there was no perforation.

Discussion

The CO_2 laser provides unique advantages for certain types of surgery. These include extreme precision of tissue ablation, with minimal postoperative pain and edema. Furthermore, the laser has intrinsic hemostatic properties.

The use of the CO_2 laser in close proximity to the airway, as during otolaryngologic surgery, places combustible endotracheal tubes at great risk for a fire, which may convert a tracheal tube into a blow-torch. This may cause fatal complications, such as major airway burns, and leave the patient without a patent tracheal airway. The use of metallic tape as a simple

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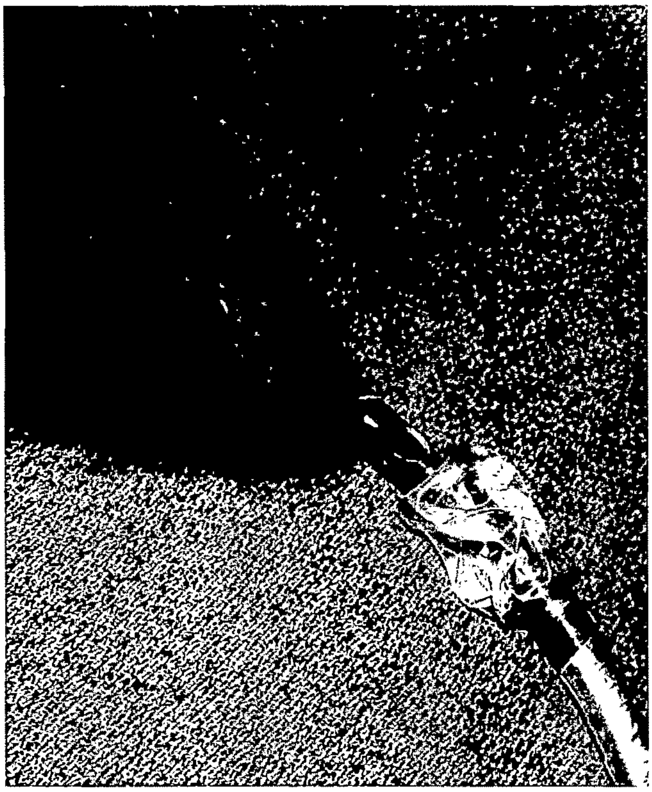

Figure 1. Endotracheal tube fire in a polyvinyl chloride tube wrapped with Radio Shack no. 44-1155 tape after contact with a CO_2 laser.

technique to protect these tubes has been suggested, although the type of tape used often was not specified (2,7,8) or an ineffective type was advocated (6).

Our results show that the type of metallic tape used to protect combustible endotracheal tubes is critical. Radio Shack tape no. 44-1155, 3M tape nos. 1430 and 433 offer inadequate protection of flammable endotracheal tubes and should not be used for this purpose. Patel and Hicks (9) reported similar results for the Radio Shack tape no. 44-1155. Copper foil tape and 3M tape no. 425 provided excellent protection of the endotracheal tubes. We, therefore, recommend their use during CO_2 laser surgery in proximity to the airway. The malleability of the copper foil allows for smoother contour than the 3M tape no. 425. The possibility of changes in the composition of any tape requires that every batch of tape be evaluated for its incendiary characteristics (3). In the evaluation of metallic tape, the laser beam must be directed at the adhesive side of the tape because some tapes, such as Radio Shack tape no. 44-1155, have an inner plastic layer that is highly flammable. This would not be detected if the laser beam was focused on the center of the tape. The impingement of the laser beam onto the edge of the tape, however, could cause a tube fire.

None of the tapes studied here are manufactured for medical applications, nor to our knowledge, have such use been sanctioned by the Food and Drug Administration. One manufacturer, when questioned, cautioned against the use of aluminum tape for medical uses (10). However, the use of protective metal tape during laser surgery is widely advocated in the literature (2–8). Metallic tape provides protection only from the direct impact of the laser beam. Indirect combustion due to sparks or heat from combustion is still possible (11), since the endotracheal tubes used are generally combustible and usually have an enriched concentration of oxygen flowing through them. Furthermore, a case of airway obstruction from metallic tape that came loose from a wrapped endotracheal tube has been reported (12).

Endotracheal tubes wrapped with 3M tape no. 425 and copper foil tape have been gas-sterilized without affecting their ability to withstand the CO_2 laser's impact, thus allowing a sterile tube to be used in clinical practice.

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Interpleural Bupivacaine for Mammography During Needle Localization and Breast Biopsy

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Key Words: ANESTHETIC TECHNIQUES, REGIONAL: interpleural.

Interpleural administration of bupivacaine is a new technique for the management of chest wall and upper abdominal pain (1–3). This technique has been shown to provide postoperative analgesia but not anesthesia sufficient for surgery (4). We report the use of this technique as a complete anesthetic, not only during mammography for needle localization (M+NL), but also for subsequent surgical excision of the breast lesion.

Case 1:

This healthy 69-year-old woman was scheduled for M+NL and biopsy of calcifications in the upper quadrant of the right breast. She weighed 70 kg and wore a 40B brassiere. Following placement of an intravenous line, BP cuff and ECG leads, the patient was placed prone with her right arm to her side. Her right upper thorax was cleansed and draped. Superior to the 3rd rib, 10 cm lateral to the spine, a skin wheal was raised with 1% lidocaine. An 18 g modified Houstead needle was advanced to the intercostal membrane at a 90° angle with the bevel directed toward the right shoulder. After removing the stylet a glass syringe filled with 2 ml air was attached to the needle and advanced until the parietal pleural was perforated and the plunger was spontaneously pulled inward. The epidural catheter was passed through the needle 6 cm into the interpleural space. The needle was then withdrawn and the catheter secured with a sterile dressing. The patient was then positioned on her right side in the head-down position. Thirty-three ml 0.5% bupivacaine with epinephrine were injected without change in heart rate or blood pressure. She remained in the lateral position for 30 minutes, the first 15 minutes of which were both lateral and head-down. Thirty minutes after injection, she had analgesia to pin prick from T3 to T9 over her right breast. The patient was asked to rank discomfort for each procedure on a visual analogue scale (VAS) 0–10 (10 = most painful). She gave mammography of the anesthetized breast a VAS of 1.5, of the unanesthetized breast a VAS of 7.5, and her initial screening mammography, a VAS of 6. No pain was experienced on insertion of the localization needle. Two hours after interpleural bupivacaine injection, breast biopsy was performed. During the biopsy she needed neither local anesthetic from the surgeon, nor sedatives or narcotics. She had only one brief twinge of discomfort (VAS = 2) and felt no pain. A chest x-ray taken in the recovery room was negative for pneumothorax.

Case 2:

This 55-year-old woman with right breast perialreolar calcifications weighed 55 kg and wore a 36B brassiere. The interpleural catheter was inserted as in Case 1. She received 25 ml 0.5% bupivacaine with epinephrine and 40 min. later had anesthesia from T3 to T10. She remained in the lateral position for one hour, the first 20 min. of which were 20° head-down. She had no discomfort during M+NL (VAS = 0) and ranked her initial screening mammogram a VAS of 5. Surgery was begun 3 hours after the injection; VAS was 0. She, too, needed neither sedatives, narcotics nor local anesthesia. Follow-up chest x-ray was normal.

Case 3:

A 55-year-old healthy, postmenopausal woman had calcifications in the upper outer quadrant of her right

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breast, weighed 68 kg and wore a size 38A brassiere. Using the technique described above, the interpleural catheter was inserted, however, in a different site. It was inserted superior to the fifth rib in the posterior axillary line, with the bevel pointing cephalad and posteriorly. The patient positioned herself right lateral decubitus with the bed 20° head-down and 25 ml 0.66% bupivacaine with 1:200,000 epinephrine was injected through the catheter. After 30 minutes in the lateral head-down position the patient was analgesic to pin prick over her right breast. She ranked mammography of the anesthetized breast, VAS = 4, because of pinching at the T1 parasternal area. Compression of her unanesthetized breast in the mammography device was ranked VAS = 10. Two hours after interpleural bupivacaine injection breast biopsy was performed. Except for two brief episodes of discomfort (VAS = 2), the patient experienced no pain. She received no sedatives, narcotics or local anesthetic. Postoperative chest x-ray was normal. By telephone follow-up 24 hours later, the patient stated she had been pain-free for 10 hours after surgery.

Discussion

With the advent of aggressive screening for breast cancer, more women are presenting for mammography with needle localization and breast biopsy. Many complain of pain during mammography, which requires firm compression of the breast between two rigid plates. A recent study of the incidence of pain during a brief (<1 minute) screening mammography and found that 39% of the patients experienced mild discomfort, 9% experienced moderate discomfort, 1% complained of severe discomfort and 1% had moderate pain (5). No study has assessed pain during M+NL, a procedure in some institutions requiring 20 to 60 minutes of breast compression.

Since the initial report of interpleural anesthesia by Reiestad and Stromskag (1), several studies have shown its effectiveness following cholecystectomy (1,3), rib fractures (2), and thoracotomy (6). Other reports have evaluated the safety of interpleural catheters. Pneumothorax has been reported in a few patients, but none have required treatment (2,3). Systemic levels of bupivacaine have been reported to be well below toxic levels except in cases with pleural inflammation (7). Because the mechanism by which interpleural injection of local anesthetics relieves pain has not been established, there is also concern of epidural spread, phrenic nerve paralysis, or block of the thoracic sympathetic chains.

Our three patients had excellent analgesia for M+NL as well as anesthesia for their breast biopsies. None had detectable adverse systemic effects or pneumothorax on post-operative x-ray of the chest. The patients had no orthostatic hypotension and had no evidence of phrenic nerve paralysis. They were able to ambulate 40 minutes after injection and to cooperate with mammography procedures. Based on our present experience it is important to position the patient in lateral head-down position before and during injection of the anesthetic and to maintain the lateral position for at least 30 min. Although dose response was not studied in these three cases, it appears that 25–35 ml of local anesthetic are needed to obtain adequate distribution. We feel that further study is required to establish the importance of catheter placement and reliability of this technique in providing good surgical anesthesia.

We present three cases in which the interpleural administration of bupivacaine provided significant pain relief during mammography for needle localization as well as anesthesia for breast biopsy. We feel that this technique may provide a safe and effective method for pain relief in this setting.

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Serum Inorganic Fluoride Levels After Enflurane In Children

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Key Words: ANESTHETICS—VOLATILE: enflurane. ANESTHESIA—PEDIATRIC.

Several recent reports have advocated use of enflurane as an inhalation anesthetic in pediatric patients (1,2). Because the cardiac arrythmogenicity of enflurane is less than that of halothane, enflurane may possess properties that make it the preferred anesthetic for pediatric otolaryngology (1). In addition, it is preferred in such procedures because enflurane is associated with a significantly more rapid emergence in children as compared with halothane and isoflurane (2), an attribute that may be beneficial for airway protection during emergence from upper airway surgery.

In humans, the majority of enflurane is excreted unchanged in the exhaled air (3). Of the portion of enflurane that is biotransformed and defluorinated, only a small amount ends up as inorganic fluoride (3). However, it is the inorganic fluoride that is responsible for the nephrotoxic effect associated with enflurane. Cousins et al. (4) have shown that the mean peak serum inorganic fluoride level in adults is 22.2 ± 2.8 μM 4 hours after an average 2.7 ± .3 maximum allowable concentration (MAC) hours of exposure to enflurane. Mazze et al. (5) found that an average serum inorganic fluoride level of 15 μM resulted in a 25% reduction in maximum urine concentrating ability in adults.

When Stoelting and Peterson (6) investigated serum inorganic fluoride levels in children after methoxyflurane anesthesia, they discovered them to be lower than in adults (21.6 versus 43.9 μM). Although, peak level occurred at 24 hours in children as in adults, blood samples were not obtained in their study between 5 and 24 hours after methoxyflurane exposure and so an earlier peak might have been missed.

Because of the progressive maturation of renal function in children with age and the absence of information on serum inorganic fluoride levels that result in nephrotoxicity in children, the present study was designed to investigate serum inorganic fluoride levels in children after enflurane anesthesia. Since glomerular filtration rate (GFR) does not achieve stable levels until 1 year of age (7), children younger than 1 year were excluded.

Methods

This study was approved by the Committee for the Protection of Human Subjects at the Dartmouth-Hitchcock Medical Center. Informed written consent was obtained from the parents of children.

Eight healthy male children aged 1 to 9 years (mean age 5) and ASA physical status I scheduled for elective ear, nose, and throat (ENT) surgery were studied. They had received no anesthetic in the previous 12 months and were taking no medications.

Anesthetic induction was with either 5% rectal methohexital (25 mg/kg) or intravenous thiopental (4 mg/kg) and facemask 70% nitrous oxide (N_2O) 30% oxygen (O_2) mixture. A venous blood sample for measurement of baseline serum fluoride levels was drawn at this point. After baseline samples were obtained, enflurane anesthesia was begun and all patients were intubated with intravenous succinylcholine (1 mg/kg). Enflurane/N_2O/O_2 with spontaneous ventilation was the maintenance anesthetic technique.

Once anesthetized, an indwelling, heparinized venous catheter was placed in the external jugular or an antecubital vein for postanesthetic blood samples 1, 3, and 6 hours after the discontinuation of enflurane anesthesia. Serum samples were frozen (−70°C) until analysis. Analysis was performed with an Orion Model 94-09 fluoride electrode (8). Since adult serum

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Table 1. Serum Inorganic Fluoride Levels (μM) After Enflurane Anesthesia in All Patients.

Age (years)	Control	1 Hour	3 Hours	6 Hours
1	2.40	14.50	5.50	4.50
2	2.10	13.00	4.50	2.50
3	2.00	14.00	12.00	4.40
5	1.60	10.50	6.00	3.00
6	1.80	8.50	3.50	2.30
7	1.30	6.90	5.50	4.00
8	1.20	12.00	4.00	3.50
9	1.30	4.40	3.60	2.50
Mean ± S.D.	1.7 ± 0.4	10.5 ± 3.6	5.6 ± 2.8	3.3 ± 0.9

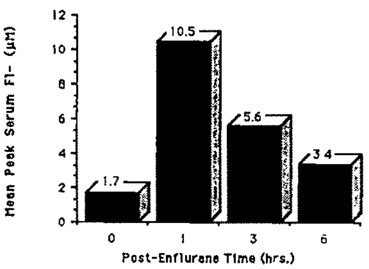

Figure 1. Mean peak serum inorganic fluoride levels for 6 hours after enflurane anesthesia.

inorganic fluoride levels peaked at 4 hours after enflurane anesthesia and previous work with pediatric bromide levels demonstrated earlier peaks after halothane than in adults, it was decided to measure fluoride levels only for 6 hours after exposure to enflurane. Enflurane dose was calculated as minutes percent, which is the sum of the products of the vaporizer settings (F_i) and the minutes at each setting.

Statistical methods included calculation of the mean and standard deviation for serum inorganic fluoride levels in baseline samples in samples obtained 1, 3, and 6 hours after enflurane administration (Table 1). Correlation coefficients (*R*) were determined by simple linear regression analysis for enflurane dose and peak serum fluoride level, for age and peak serum fluoride level, as well as for age and enflurane dose. In addition, 95% confidence bands are described for all linear regression lines.

Results

Individual serum inorganic fluoride levels in all eight children at all four times, as well as mean values, are given in Table 1. As seen in Figure 1, the mean peak serum fluoride value of 10.5 ± 3.6 μM occurred 1 hour after enflurane anesthesia was discontinued. By 6 hours after enflurane, values were returning toward control levels.

From Figure 2, it can be seen that as the dose of enflurane (Σ F_i enflurane × time) increased so, too, did the peak serum fluoride level (*R* = 0.82). Cousins et al. (4) found no correlation (*R* = 0.55) between enflurane MAC hours and peak serum inorganic fluoride levels in their 10 adult patients.

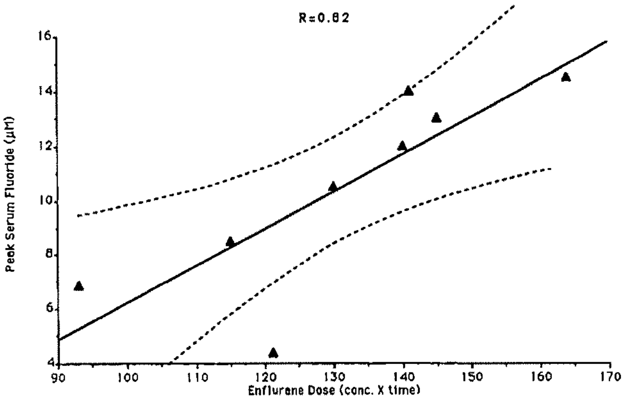

Figure 2. Peak serum inorganic fluoride levels as a function of total enflurane (Σ F_i enflurane × time). [Regression analysis with 95% confidence bands for true mean of Y.]

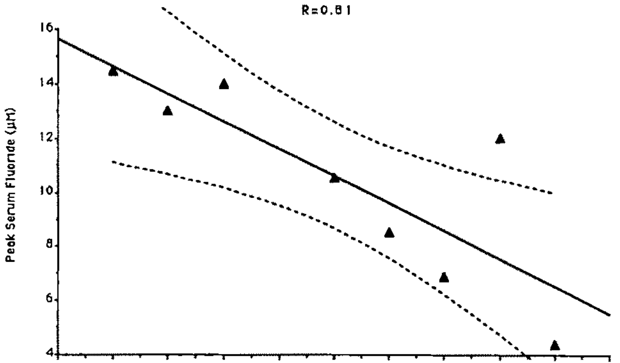

Figure 3. Peak serum inorganic fluoride levels as a function of age. [Regression analysis with 95% confidence bands for true mean of Y.]

When age and peak serum inorganic fluoride levels were compared (Fig. 3), there was an inverse relation (*R* = 0.81). The three patients aged 1 to 3 years had higher peak serum fluoride levels than the five older children. Figure 4 depicts the relation between enflurane dose and patient age (*R* = 0.68), indicating that the age/peak serum fluoride relation appears not to be due to simply larger enflurane doses received by the younger patients.

Discussion

When Stoelting and Peterson (6) reported lower peak serum inorganic fluoride levels after methoxyflurane in children than in adults, they offered four possible

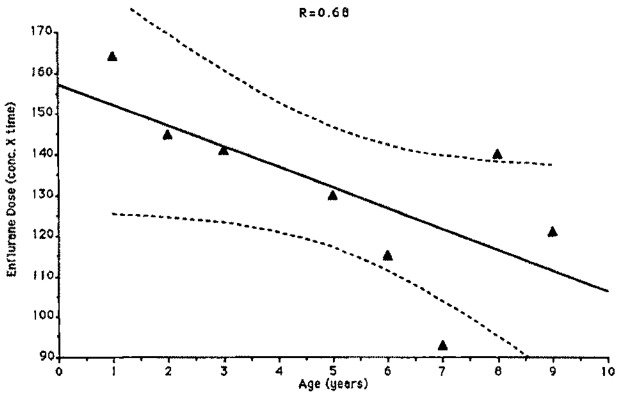

Figure 4. Total enflurane (Σ F_i enflurane × time) as a function of age. [Regression analysis with 95% confidence bands for true mean of Y.]

explanations: slower metabolism, increased renal clearance, increased bone deposition, and more rapid postoperative pulmonary elimination. In the present study, peak serum inorganic fluoride levels after enflurane anesthesia in children resulted in earlier but lower peaks than in adults, as reported by others.

Slower metabolism due to an immature hepatic microsomal enzyme system involved in enflurane metabolism seems a highly unlikely explanation for the present findings. Although the premature neonate may have impaired ability to metabolize certain drugs (9), there is no evidence to suggest that older healthy children have impaired hepatic levels of enzyme involved in drug metabolism. In fact, most evidence suggests enhanced drug metabolism in children. Stoelting and Peterson (6) investigated children 6 to 12 years of age and, in the current study, ages ranged from 1 to 9 years, clearly age ranges that are consistent with the presence of fully developed drug-metabolizing capacity.

Increased renal clearance of fluoride seems equally unlikely as the reason for the lower levels of inorganic fluoride in children seen in our patients. In fact, Spak et al. (10) reported the opposite (that is, that children have a lower renal fluoride clearance than adults). They also showed a relation between reduced GFR and reduced renal clearance of fluoride. Knowing that GFR in children does not reach adult values until about 1 year of age, one could argue that young children whose GFR has not matured could have higher serum fluoride levels associated with reduced renal clearance of fluoride. In the present study, the finding of higher serum fluoride levels in the younger children (Fig. 3) may support this concept. As Schwartz et al. (11) have shown, GFR can be estimated by body length in children, indicating the progression of renal maturation as the child grows. Although we believe renal development and GFR maturation to be complete by at least 1 year of age, there may be a transitional period that might have some influence on renal clearance of fluoride for the first few years of life.

The possibility that increased bone deposition of fluoride in children accounts for the present findings is the most intriguing. In young mice, Fiserova-Bergerova and Phillips (12) reported that enflurane exposure resulted in a 50% increase in skeletal fluoride. All children have an active skeletal system, and the skeletal storage pool for fluoride probably increases greatly until epiphyseal closure. With enhanced bone deposition of fluoride, the result would be lower serum levels. However, how can we explain the higher serum fluoride levels in the younger patients who presumably also have very active bone growth? Perhaps their total skeletal mass has not reached a critical value to allow for rapid and complete fluoride deposition. Although this seems to be an enticing explanation, there may be another one, namely, that in the three patients aged 1, 2, and 3 years in this study, it was retrospectively discovered that they were being given fluoride supplementation for prevention of dental caries. The question arises as to whether these three patients had a relative impairment in their ability to deposit further ions in an already fluoride-saturated skeletal system. If this were the case, it could account for the apparent higher serum inorganic fluoride levels in the younger children.

Although the present study demonstrated lower serum inorganic fluoride levels in children after enflurane anesthesia, the finding of higher levels in the 1 to 3 year old children needs further investigation. Even though serum fluoride levels of 13 to 14.5 μM appear to be well below the nephrotoxic ranges described in the literature, it must be remembered that, especially in the first year of life, renal maturation may be incomplete. Further investigation in the premature, neonate, and child younger than 1 year would be helpful.

In summary, serum inorganic fluoride levels were measured in eight children, 1 to 9 years of age, for up to 6 hours after enflurane anesthesia. Peak serum inorganic fluoride levels occurred at 1 hour after enflurane anesthesia, with a mean peak value of 10.5 μM (range 6.9 to 14.5). Compared with adult data, the peak fluoride levels occurred earlier (1 versus 4 hours, respectively) and were of reduced value (10.5 versus 17 μM). The younger the child, the higher the peak fluoride level (14.5 μM at 1 year versus 4.4 μM at 9 years). Decreased renal clearance of fluoride and enhanced bone deposition of fluoride may explain these findings in children.

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Acute Bronchospasm Complicating Intercostal Nerve Block with Phenol

Gary L. Atkinson, DO, and Robert C. Shupak, MD

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—intercostal block. ANESTHETICS, LOCAL—phenol.

Intravascular injection of local anesthetics or neurolytic agents and pneumothorax have been described as complications of intercostal nerve block (1–3). To our knowledge acute bronchospasm associated with intercostal neurolytic nerve block with phenol has not been described. We present such a case and discuss possible causes of this complication.

Case Report

A 51-year-old male with adenocarcinoma of the lung underwent a right upper and middle lobectomy. During resection, the lung was found to be adherent to the posterior chest wall and this area was partially resected as well. He was referred to our pain service approximately 6 months after surgery because of increasingly severe radiating chest wall pain. The patient had significant pain relief after each of two local anesthetic intercostal nerve blocks with bupivacaine, and subsequently was scheduled for neurolytic nerve block with phenol. Because diagnostic and therapeutic evaluations of the chest wall pain were simultaneously in progress, we were asked to avoid the injection of solutions containing radioopaque materials.

The patient was placed in a prone position on the operating table, the ECG and non-invasive blood pressure were monitored and an intravenous infusion was started. The area of the posterior chest wall was cleansed with an antiseptic solution and draped. Two syringes were prepared and labeled, one with sterile 2% lidocaine, the other with 8% phenol in normal saline solution. The third, fourth, and fifth rib angles were identified by palpation and a needle placed into the fourth intercostal space as described by Moore, using an immobile needle technique (3,4). Three milliliters of lidocaine were injected and satisfactory chest wall hypesthesia was obtained. Then, 3 ml of phenol solution were injected through the same needle. Neither air nor blood could be aspirated through the needle prior to each injection. The same procedure was carried out at the fifth and third intercostal space. After approximately 2 ml of phenol were injected into the third intercostal space, the patient coughed and injection was halted. After a negative aspiration test the injection was resumed. The patient complained that he tasted phenol and had a burning sensation in his pharynx. The injection was immediately halted, but not until approximately 0.5 ml of phenol solution had been injected. The needle was withdrawn.

The patient became tachypneic. Auscultation of the chest revealed bilateral inspiratory and expiratory wheezing and rhonchi. The patient expectorated tenacious sputum which had a faint odor of phenol. Examination of the pharynx was unremarkable. The patient was treated with an albuterol inhaler which decreased the bronchospasm. He complained of itching around the injection site and there was a mild erythematous flush over his shoulders and neck. His vital signs remained stable. The patient was transported to the recovery room for observation. Following bronchodilator treatment with albuterol the respiratory symptoms and signs eventually resolved, including the pharyngeal soreness. Chest x-ray revealed no pneumothorax or pneumonitis. A complete blood count was within the normal range. The IgE level was normal. The patient was discharged to home care and followed as an outpatient. The following day, the patient developed a mild hoarseness which persisted for approximately one week. Chest x-ray, one week after the incident, was unchanged and the residual symptoms continued to resolve. The

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chest wall pain was diminished to a tolerable level by the neurolytic nerve block.

Discussion

This patient with a diagnosis of carcinoma of the lung developed chest wall pain presumably due either to tumor invasion of the chest wall or postoperative neuroma formation after thoracic surgery with chest wall and lung resections. Neurolytic intercostal nerve block was chosen for this patient after successful, but temporary, relief of pain with local anesthetic injections on two previous occasions. Medications such as narcotics and tricyclic antidepressants might have been useful in this situation, but our patient felt these to be unacceptable alternatives.

Intercostal nerve block in experienced hands has a low complication rate (3). Complications include hypotension, total or partial spinal anesthesia, pneumothorax, and intravascular injection (3,4). These complications can be minimized by aspiration after careful needle placement. Phenol solution, when used for intercostal blockade, may produce tissue necrosis, hyperesthesia, dysesthesia, pleural irritation and effusion, and nerve damage (1).

In the present case, symptoms of intravascular phenol injection did not occur. These include severe tinnitus, flushing, and CNS stimulation. The tinnitus and flushing usually resolve completely and rapidly, but the CNS stimulation may cause muscle tremors and convulsions.

Possible etiologies of bronchospasm in this patient include an allergic reaction and inadvertant intrabronchial or intrapulmonary injection of phenol. An allergic reaction appears unlikely in this case, since other associated systemic and cutaneous indications such as a decrease in blood pressure, a change in heart rate, and the appearance of a rash did not occur. This observation is supported by an eosinophil count that was normal and the absence of elevation in the IgE level. An allergic response also does not readily explain the pharyngeal burning and the taste of phenol that the patient experienced. Intrabronchial or intrapulmonary injection of phenol is irritating to the respiratory mucosa, and would be expected to cause an increase in airway secretions, coughing, pharyngeal burning, and bronchospasm. The bronchospasm responded to initiation of bronchodilator therapy and did not progress to deterioration in respiratory status requiring intubation.

The absence of a pneumothorax in this patient following a presumed intrapulmonary or intrabronchial injection may be explained by the fact that the patient had a resection of the superior-posterior chest wall, and this probably caused adhesions in the area that prevented pneumothorax. The resection also may have decreased the potential space between the intercostal musculature and the parietal and visceral pleura, thereby predisposing the patient to intrapleural or intrabronchial injection. A computerized axial tomographic scan of the thorax in the region of injection at the third rib showed some irregularity of the chest wall postoperatively, which supports this possibility. The absence of pneumonitis is, however, surprising considering the effect of phenol on tissues. This suggests that the amount of phenol actually injected intrabronchially was minimal. A CAT scan of the thorax 4 weeks after neurolytic block was unchanged except for an increase in size of the tumor.

To our knowledge, bronchospasm after neurolytic intercostal nerve block with phenol has not previously been described. The risk of this and other reported complications would be increased in any patient who undergoes transcutaneous needle placement for intercostal nerve block after thoracotomy, traumatic injuries involving the chest, or surgical resection of the chest wall as in this case. In addition, the negative aspiration test before and during injection may not aid in assuring the proper positioning of the needle in the intercostal space. The confirmation of correct needle placement using contrast dye radiography may be helpful in these cases, especially when injecting neurolytic agents.

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Consecutive Cardiac Arrests on Induction of Anesthesia Associated with Nifedipine-Induced Carotid Sinus Hypersensitivity

Charles N. Plotkin, MD, Paul D. Eckenbrecht, MD, and Douglas A. Waldo, MD

Calcium channel blockers have gained widespread use for their specific electrophysiologic and hemodynamic effects (1). Their coronary vasodilating and inhibitory electrophysiologic properties are important in the treatment of the patient with ischemic cardiac disease (2,3). With the increasing frequency, the vasodilating properties of these drugs, especially nifedipine, are being used to control both acute and chronic hypertension in patients with no known ischemic cardiac diseases (4,5). The following case report provides an example of carotid sinus hypersensitivity related to chronic calcium channel blocker use in an otherwise asymptomatic patient. The impact of this autonomic dysfunction is evidenced by two sequential cardiac arrests associated with induction of general anesthesia.

Case Report

A 62-year-old, 70-kg woman was scheduled for elective cholecystectomy. Past medical history was significant for hypertension, borderline diabetes, cholelithiasis, and a 40-pack per year smoking history. The hypertension was well-controlled with blood pressures of 130–160/80 mm Hg on a regimen of nifedipine 10 mg orally three times a day. An oral hypoglycemic agent had been discontinued six days prior to surgery. The patient's previous surgical history included six general anesthetics without complications. The patient's preoperative EKG, chest x-ray, and laboratory data, including electrolytes, were unremarkable except for a blood glucose of 156 mg/dl.

Preoperatively, the patient was medicated with oral diazepam 10 mg, an oral antacid, and her morning dose (10 mg) of oral nifedipine. Additional sedation with midazolam (1.25 mg IV) was given after establishing intravenous access. The patient was preoxygenated by face mask as monitors were applied, including EKG, automated sphygmomanometer, pulse oximeter, and precordial stethoscope. After 5 min of preoxygenation, the patient was given fentanyl 100 μg, d-tubocurarine 3 mg, and lidocaine 75 mg IV. Vital signs were stable, blood pressure 134/67 mm Hg, heart regular at a rate of 70 bpm, and oxygen saturation of 98%. Anesthesia was induced with thiopental (250 mg IV) with succinylcholine (100 mg IV) given 60 seconds later. Sellick maneuver was maintained without manual ventilations. After loss of consciousness, vital signs were blood pressure 110/60 mm Hg and heart rate of 65 bpm. Laryngoscopy was attempted unsuccessfully, and the patient was easily ventilated by face mask. Oxygen saturation was 96%. Within one minute the heart rate decreased to 40 with a wide sine wave QRS pattern. There was no response to 0.5 mg IV atropine. Cardiopulmonary resuscitation (CPR) was started in the absence of carotid or peripheral pulses, and atropine 0.5 mg IV was repeated. The QRS complex remained widened with a heart rate of 40. Dextrose (25 g), sodium bicarbonate (50 mEq), regular insulin (10 μg) and calcium chloride (1 g) were given IV. The patient was then intubated. The pulse oximeter indicated an oxygen saturation of 87% with each chest compression. The QRS complex remained wide with a heart rate of 50 bpm with no peripheral pulse palpable. A venous blood sample returned from the lab (obtained prior to administration of dextrose and calcium chloride) had a potassium level of 3.9 mEq/L. An arterial catheter was inserted, and 1 mg of epinephrine was administered IV without effect. CPR was continued for no pulses and an arterial blood sample had a pH of 7.25, PO_2 of 154 mm Hg, PCO_2 of 54 mm Hg,

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HCO_3^- of 22.9 mEq/L, base excess −4.7 mEq/L. Chest auscultation was normal. No pneumothorax was seen on x-ray. Repeat doses of atropine, epinephrine, calcium, and sodium bicarbonate were given. Peripheral and carotid pulses returned with a heart rate of 60 bpm, which soon increased to 150 bpm with a blood pressure of 160/90 mm Hg. The patient developed ventricular tachycardia that reverted to sinus tachycardia with a precordial thump and 100 mg of lidocaine IV. The heart rate stabilized at 110 bpm (sinus tachycardia), with a blood pressure of 134/90 mm Hg, and an arterial pH of 7.16, a PCO_2 of 65 mm Hg, a PO_2 of 202 mm Hg, and a HCO_3^- of 21.9 mEq/L. The patient then developed severe expiratory wheezing. She was awake and attempted to extubate herself. Blood pressure was 180/90 mm Hg with a pulse of 110 bpm. The patient was given 50 μg of fentanyl IV and the blood pressure decreased over the next three minutes to 60/30 mm Hg. Ephedrine 20 mg was given IV, and blood pressure increased to 130/90 mm Hg, pulse 110 bpm with continued expiratory wheezing. The patient responded to verbal commands and had a tidal volume of 250 ml. Aminophylline (250 mg in 250 ml of 5% dextrose in water solution) was given IV slowly. The patient was extubated and surgery cancelled. The wheezing cleared with extubation. On admission to the recovery room, arterial pH was 7.36, PCO_2 45 mm Hg, PO_2 254 mm Hg, respiratory rate 20, blood pressure 114/74 mm Hg, pulse 74 bpm. She had no EKG or isoenzyme evidence of myocardial infarction.

A cardiology consultant suggested the possibility of right carotid hypersensitivity based upon a 15-beat decrease in heart rate (70 to 55) during carotid sinus massage. Neck manipulation and vasovagal reaction to the stimulus of intubation was felt to be responsible for the severe bradycardia and electromechanical dissociation. Treatment with anticholinergic drugs before induction of anesthesia was recommended, as was prophylactic temporary cardiac pacing preoperatively even though permanent pacing was not felt necessary in this otherwise asymptomatic patient.

The patient returned to surgery three weeks later for her cholecystectomy. She was premedicated with midazolam 5 mg IM, ranitidine 150 mg orally, an oral antacid, and her morning dose of nifedipine 10 mg orally. Preoperative blood pressure was 170/60 mm Hg and pulse rate 70–75 bpm. Two peripheral intravenous and an arterial catheters were inserted after midazolam 3.0 mg IV. The upper airway was sprayed with 5% lidocaine. During denitrogenation with oxygen, atropine 1.0 mg was given with a resulting increase in heart rate to 85 bpm from 75. Additionally, glycopyrolate 0.4 was given, which increased the heart rate to 90 bpm from 85. Induction proceeded with thiopental 175 mg IV in divided doses, and enflurane in 0.5% increments with spontaneous ventilation. No positive airway pressure or cricoid pressure was given. At 1.5% enflurane, the patient coughed once which resulted in a decrease in heart rate to 50 bpm from 90, with a rapid decline in systolic blood pressure to 70 mm Hg. As systemic blood pressure and heart rate continued to decrease, CPR was instituted, and ventilation by mask with 100% oxygen was easily maintained. An isoproteronol infusion was started without effect and the enflurane was discontinued. The patient was orally intubated and a left subclavian catheter was inserted. A transvenous pacemaker was placed allowing asynchronous ventricular pacing without discernible systemic pressure. After 1.5 mg of epinephrine IV and 1.0 gram of calcium chloride IV, the patient developed an intermittent accelerated idioventricular rhythm of 110–120 bpm with a systolic blood pressure of 90 mm Hg. An epinephrine infusion was started at 1 μg/min and increased to 8 μg/min. In spite of a stable blood pressure, runs of ventricular tachycardia and ventricular fibrillation occurred requiring six defibrillations. Two bretylium IV injections (each 5 mg/kg), followed by an infusion at a rate of 2 mg/min, resulted in decreased ventricular irritability. Direct epicardial atrioventricular (AV) wires were then placed via sternotomy. With myocardial AV pacing, the epinephrine infusion could be decreased to 5 μg/min with a systolic blood pressure of 140 mm Hg. A pulmonary arterial catheter inserted via the subclavian introducer showed a cardiac index of 3.5 liters/min, pulmonary artery occlusion pressure of 20 mm Hg, pulmonary artery pressure of 45/22 mm Hg, and calculated pulmonary vascular resistance of 500 $dyne \cdot sec \cdot cm^{-5}$ during infusion of 5 μg/min epinephrine. Epinephrine was discontinued and phenylphrine 2 μg/min started. The patient was transferred to the intensive care unit with a systolic blood pressure of 100 mm Hg and a heart rate of 110–120 bpm, where she was mechanically ventilated for 24 hours.

The patient recovered completely. Subsequently, she underwent intradermal skin tests using thiopental (negative), midazolam (negative), and normal saline (negative). A curare skin test was positive without evidence of anaphylaxis, but a definite histamine response to d-tubocurarine. Echocardiography showed the left ventricle to be normal with normal wall motion and with valves normal in appearance and function. There was no evidence of obstructive cardiomyopathy. Carotid sinus massage studies after nifedipine had been discontinued showed normal sinus slowing with a slight decrease in blood pressure. After 10 mg of sublingual nifedipine, carotid sinus massage resulted in a 7.5-second sinus arrest with junctional escape at 38 to 40 bpm. Systolic blood pressure decreased from 140 to 86 mm Hg during slowing. It was concluded that the patient had significant vasodepressor effect with increased vagal tone while on nifedipine therapy. Nifedipine was discontinued and clonidine started to control her hypertension.

Discussion

Rovenstine reviewed the anesthetic management of 3 patients with hyperactive carotid sinus reflexes in 1939 (6), including one case of intraoperative cardiac arrest in a patient pretreated with scopolamine who immediately recovered when procaine was used to anesthetize the left carotid sinus. The other two cases were patients who developed severe bradycardia that responded primarily to local anesthetic of the carotid sinus. A more recent review of five cases of symptomatic carotid sinus syndrome also includes a patient who developed intraoperative cardiac arrest (7). The case report presented here compliments previous reports in two important ways: 1) induction and maintenance of anesthesia in patients with carotid sinus syndrome can be a potent stimulus to triggering of intraoperative cardiovascular collapse not easily treated with standard therapy, and 2) the preoperative medical regimen including nifedipine exaggerated this response in an otherwise asymptomatic patient.

The carotid sinus syndrome (CSS) is usually present with a history of spontaneous attacks of dizziness and near fainting (5). The patient may experience loss of consciousness or convulsions. These symptoms are frequently reproduced with gradual pressure on the sinus or change in position of the head and neck. The hyperactive carotid sinus reflex is demonstrated clinically when carotid sinus massage results in either a ventricular asystole lasting 3 sec or longer, or a decrease in the systolic blood pressure of at least 50 mm Hg. The reflex is thought to be most evident in the sitting or upright position.

Three forms of CSS have been described (7). One, the cardioinhibitory form, is present in 79% of affected individuals, presents with sinus bradycardia, AV block, or both. It is only minimally responsive to atropine. The second form, present in 10% of CSS patients, is a vasodepressor effect with hypotension and no bradycardia. Historically, a third type is described where syncope develops, not related to changes in blood pressure or heart rate. The existence of this cerebral form is currently debated. The additional 20% of patients display a mixed combination of the cardioinhibitory and the vasodepressor reflex.

Afferent nerve impulses from the carotid sinus are carried primarily by the glossopharyngeal nerve, but some may also be carried by the hypoglosssal and cervical sympathetic nerves (6). These impulses are carried to the autonomic centers in the medulla with efferent pathways via the vagus nerve and sympathetic nervous system. Elevation of blood pressure stimulates stretch receptors in the carotid sinuses causing reflex decrease in sympathetic outflow and increased parasympathetic tone. The increase in parasympathetic tone is responsible for the decrease in heart rate, myocardial contractility, and increased AV nodal conduction time.

Treatment of hyperactive carotid sinus syndrome varies from patient to patient (6). Some patients are able to do well by avoiding rapid neck movements and tight collars. Antimuscarinic therapy may be helpful in abolishing the vagal tone but has no appreciable effect upon the depressor or cerebral types of reactions. Cardiac pacemakers can help correct abnormalities of heart rate but have no effect on the depressor reflex. Epinephrine and ephedrine may be used to treat both vagal and depressor responses but are ineffective in treating the cerebral type of CSS. Rovenstine describes a therapeutic and diagnostic carotid sinus nerve block technique that may prevent all types of responses in CSS patients (6). Irradiation and surgical ablation can also be considered to intercept the afferent reflex limb. It should be noted that sinus nodal dysfunction is not a major concern.

The patient described in this case report was unwilling to undergo invasive cardiac electrophysiologic studies. It is unclear how the nifedipine promoted hypersensitivity of the carotid sinus, but it appears that induction of anesthesia did trigger a combined cardioinhibitory/depressor reflex. Standard pharmacologic treatments of her cardiovascular collapse were ineffective, requiring primarily direct cardiac pacing with potent vasoconstrictors. In retrospect, discontinuation of the nifedipine, and perhaps blockade of the afferent carotid sinus limb may have prevented triggering of this life-threatening autonomic dysfunction.

In conclusion, carotid sinus hypersensitivity should be recognized as a potent aberrant clinical response. In this patient, carotid sinus hypersensitivity was associated with the use of oral nifedipine.

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Sixty-Six Years Ago In
Anesthesia & Analgesia

Brown, W. C.: Preliminary report on experiments with ethylene as a general anesthetic, p. 117
Luckhardt, A. B.; Carter, J. B.: Ethylene as a gas anesthetic, p. 221
Herb, I. C.: Ethylene: Notes taken from the clinical record, p. 230
Current Researches in Anesthesia and Analgesia: 1923; Vol. 2.

These articles herald the introduction of ethylene, the first inhalation anesthetic to achieve any significant recognition in the 75 years or so since the introduction of chloroform by Simpson. What initially called ethylene to the attention of scientists was the demonstration that the closing of flowering carnations in greenhouses exposed to leaking illuminating gas was due to the effects of ethylene in the gas. This led to experiments on ethylene in a variety of plants and animals (yes, anesthetics affect plants too) that culminated in publication of articles by the authors cited above showing that ethylene was an effective inhalation anesthetic. Brown, author of the first of the three papers, was an anesthetist at Toronto General Hospital who worked with Velyen Henderson in the Department of Pharmacology at the University of Toronto to define the physical characteristics of ethylene and to show that it produced anesthesia in animals when inhaled in a concentration of 80% in oxygen. Luckhardt, professor of physiology at the University of Chicago, and Carter, house officer at Presbyterian Hospital in Chicago, were simultaneously working along the same lines as was Brown. Their pharmacologic studies were more complete and detailed than Brown's, but their results were similar: 80% ethylene was anesthetic. Isabella Herb, chief of anesthesia at Presbyterian Hospital in Chicago and professor of anesthesia at Rush Medical College of the University of Chicago, was the one who established the clinical safety and usefulness of ethylene as a surgical anesthetic. It is impossible (and unnecessary) to try to determine priority for the introduction of ethylene; papers similar to these three by the same authors had appeared almost simultaneously in other journals just months earlier. Ethylene soon became widely, though never universally, used. Its principal advantage was that it provided a viable alternative to chloroform, ether, and nitrous oxide, the only other inhalation anesthetics available at the time—and one of these, nitrous oxide, was not a complete anesthetic. Ethylene administered in the same way as nitrous oxide, however, was just enough more potent than nitrous oxide to be able to produce general anesthesia in even the most robust of patients when inhaled at a concentration of 80%. It did so, furthermore, without producing adverse respiratory or cardiovascular side effects. The major disadvantage of ethylene was that it was explosive. Not only that, it was lighter than air. This meant that, unlike ether, ethylene could not be used in the presence of electrical and other sources of ignition five feet above floor level. Ethylene was still being used as an explosive but potent nitrous oxide as late as 1950, by which time it had been largely displaced by cyclopropane.

Preoxygenation: A Study of Denitrogenation

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Key Words: GASES, NON-ANESTHETIC—nitrogen. OXYGEN—pulmonary uptake. INDUCTION, ANESTHESIA—pre-oxygenation.

Controversy exists as to the most appropriate method for preoxygenation of patients prior to induction of anesthesia (1–5). The recommendations for adequate preoxygenation have varied from normal breathing of 100% oxygen for periods of 10 minutes (2) to taking four maximal breaths over 30 seconds (6). Most studies have measured oxygen saturation or content of blood rather than the actual content of nitrogen in the lungs (1–15). It is the wash out of nitrogen from the lungs that is the key to achieving adequate preoxygenation.

Recently, the four maximal breath technique of preoxygenation was found to be associated with a statistically significant shorter time to onset of oxygen desaturation of blood when compared with normal breathing of 100% oxygen for 3 minutes (8). These results suggest that the four breath technique of preoxygenation, although fully saturating hemoglobin, does not provide as complete a denitrogenation of the lungs as does 3 minutes of normal breathing of 100% oxygen.

To try to determine the basis for this difference, we used mass spectrometry to compare the effectiveness of nitrogen washout from the lungs under three different preoxygenation regimens: 1) normal tidal breathing of 100% O_2 until end-tidal N_2 was <1%; 2) maximal breathing of 100% O_2 to total lung capacity; and 3) taking eight vital capacity breaths of 100% O_2.

Methods

Nine healthy volunteers, all ASA physical status I, were studied. Four were female; five were male. All were nonsmokers. In the supine position, subjects breathed from a circle system fitted with a two liter reservoir bag. A snug-fitting face mask (Life Design Systems, Carrollton, TX) was used; alternatively, in bearded subjects, nose clips and a cut 9.5 mm ID endotracheal tube held in the mouth were used to prevent the air leak found with a mask. Flow rates were set at 10 liters/minute to prevent rebreathing. The oxygen flush was used to keep the reservoir bag filled and provide adequate flows during maximal inspirations.

After a period of tidal breathing of 21% oxygen (room air) to establish a respiratory pattern and baseline values for nitrogen and carbon dioxide, the mask was removed from the subject's face and the breathing system was flushed with 100% oxygen for several seconds to fill the tubing, reservoir bag, and CO_2 absorber with 100% oxygen. The mask was then reapplied, and the subjects were studied under three experimental conditions: 1) normal respirations until the end-tidal nitrogen content was reduced to 1% (normal tidal breathing); 2) the subjects were instructed to take eight maximal breaths to total lung capacity with passive exhalation (inspiratory capacity breathing); and 3) the subjects were instructed to exhale to residual volume and then take eight vital capacity breaths, expiring to residual volume between each inspiration (vital capacity breathing). At least 30 minutes of breathing room air was carried out between each study to re-nitrogenate the subjects' lungs.

The subjects were monitored with use of a pulse oximeter (Biox 3700, Ohmeda, Boulder, CO). A Narkomed 2A anesthetic gas machine (North American Drager, Telford, PA) was used, which provided fresh gas flow, tidal volumes, and respiratory rates. The spirometry readings were confirmed with use of a Wright respirometer (British Oxygen Co. Ltd., London, UK).

Inspired and expired gases were continuously monitored for oxygen, nitrogen, and carbon dioxide

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Table 1. Arterial Oxygen Saturation and End-Tidal Carbon Dioxide Concentrations in Nine Volunteers Before and After Breathing 100% Oxygen

	Before Nitrogen Washout	After 3 Min Tidal Breathing	After 8 Inspiratory Capacity Breaths	After 8 Vital Capacity Breaths
Sex	M:F	M:F	M:F	M:F
Number	5:4	5:4	4:2	3:3
SaO_2 (%)	97–99	100	100	100
$PETCO_2$ (%)	5.21 ± 0.24	5.14 ± 0.23		
	5.35 ± 0.13		4.51 ± 0.12*	
	5.34 ± 0.31			4.23 ± 0.25*

*$P < 0.01$ compared with baseline values by *t* test.

with use of a mass spectrometer (Advantage 2000, Perkin-Elmer, Pomona, CA) set to read each end-tidal peak, i.e., breath averaging turned off. Gas was sampled from the face mask or cut endotracheal tube at a rate of 250 ml/minute.

Data are presented as mean ± SE of the mean. Data were subjected to an Analysis of Variance with intergroup difference being determined by the least significant difference method (16).

Results

The volunteers were healthy, ASA physical status I, nonsmokers 26 to 43 years of age (33 ± 2), 175 ± 3 cm tall, and weighing 69 ± 5 kg. There was no history of respiratory or cardiac disease.

Arterial saturations were 97 to 99% while breathing 21% oxygen (room air), and 100% in all subjects while breathing 100% oxygen (Table 1). End-tidal carbon dioxide concentrations indicated that some of the nine subjects tended to hyperventilate slightly during tidal breathing. However, there was no statistically significant difference in end-tidal carbon dioxide concentrations (delta = −0.07 ± 0.09%, N = 9) before and after breathing 100% oxygen for 3 minutes. After eight inspiratory capacity breaths, there was a significant reduction in the end-tidal carbon dioxide concentrations (delta = −0.84 ± 0.13%, N = 6; $P < 0.01$) as there also was after eight vital capacity breaths (delta = −1.11 ± 0.12%, N = 6; $P < 0.01$).

The washout of nitrogen from the lungs of nine subjects during normal tidal volume breathing for 3 minutes is shown in Figure 1. Nitrogen washout occurred in an exponential fashion with 18.9 ± 2.8% remaining after 1 minute, 5.5 ± 1.5% remaining after 2 minutes, and 2.1 ± 0.7% remaining after 3 minutes of normal breathing. The time required to reach an end-tidal nitrogen concentration of 1% varied from 2 minutes and 15 seconds to 6 minutes and 30 seconds.

End-tidal nitrogen concentrations during inspiratory capacity breathing and vital capacity breathing for eight breaths are shown in Table 2. The end-tidal nitrogen concentrations declined in an exponential fashion during inspiratory capacity breathing, reaching 16.9 ± 2.5% after four breaths and 6.1 ± 1.3% after eight breaths. With vital capacity breathing, the end-tidal nitrogen concentrations declined exponentially, reaching 6.8 ± 0.7% after four breaths and 0.9 ± 0.3% after eight breaths.

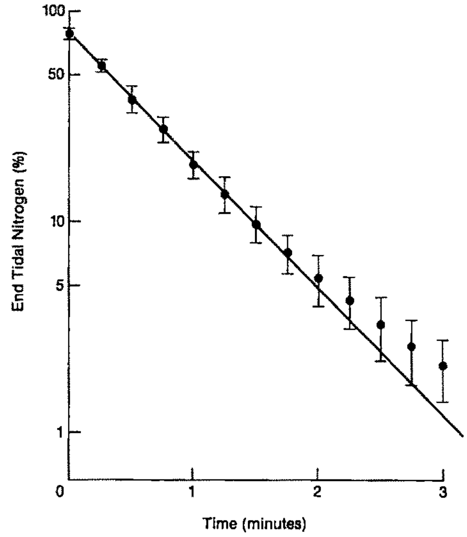

Figure 1. Logarithmic plot of % end-tidal nitrogen concentration versus time in nine subjects during tidal volume breathing of 100% oxygen. Values are mean ± SEM. The line represents the linear regression analysis of log end-tidal nitrogen from 0 to 2 minutes [R = −0.999; slope = −0.0098; Y-intercept = 1.887 (77% nitrogen)].

Discussion

Preoxygenation is a standard anesthetic technique for preventing significant hypoxemia during the induction of anesthesia. Methods of preoxygenation vary from normal breathing of 100% oxygen for periods of 2–10 minutes to taking 4 maximal breaths of 100% oxygen (2,3,8).

In studies on the preoxygenation of patients, most authors have followed the saturation of hemoglobin,

Table 2. End-Tidal Nitrogen Concentrations (%) During Control Tidal Volume Breathing of 21% Oxygen (room air) and During Eight Breaths of Either Inspiratory Capacity or of Vital Capacity of 100% Oxygen

CONTROL (room air) 21% Oxygen	Number of Breaths of 100% Oxygen							
	1	2	3	4	5	6	7	8
				Inspiratory Capacity Breathing				
80.0 ± 0.4	75.2 ± 1.7*	38.2 ± 4.5†	24.6 ± 2.8†	16.9 ± 2.5†	11.5 ± 2.1†	8.7 ± 1.8†	7.6 ± 1.5†	6.1 ± 1.3†
				Vital Capacity Breathing				
79.7 ± 0.3	79.6 ± 0.5	27.6 ± 1.3	12.5 ± 1.0	6.8 ± 0.7	3.6 ± 0.8	2.4 ± 0.5	1.3 ± 0.4	0.9 ± 0.3

*$P < 0.05$; †$P < 0.01$ compared with vital capacity values at each breath by t test.

which does not, however, provide information about the reserve of oxygen in the lung (3,4,6–11,13). It is the replacement of nitrogen by oxygen in the functional residual capacity of the lung prior to induction of anesthesia that provides the reserve of oxygen (5,12,14). Earlier studies showed that nitrogen washout occurs in an exponential fashion, reaching an exhaled concentration of 5% after 2–3 minutes of breathing 100% oxygen. This rate of washout was dependent on fresh gas flow and was reduced in the presence of an air leak in the circuit or if rebreathing occurred (12,14). These studies did not measure nitrogen washout during inspiratory capacity or vital capacity breathing.

In the present study of preoxygenation using mass spectrometry, there was still about 7% nitrogen remaining in the lungs after four vital capacity breaths. This would be a minimal value because patients taking maximal breaths would not likely achieve vital capacity breathing. Indeed in the present study, the washout of nitrogen with inspiratory capacity breathing was less with end-tidal nitrogen values of about 17% after four breaths. This residual nitrogen content in the lung may well explain part of the difference in the time to desaturation found by Gambee and coworkers (8). If a patient consumes 250 to 300 ml of oxygen each minute at rest, an 8 minute period of apnea could be tolerated in a paralyzed patient if the lung nitrogen were completely replaced by oxygen and assuming a lung functional residual capacity of about 2,500 ml. In a situation of incomplete denitrogenation to a content of 17% nitrogen in the lung, as was found after four inspiratory capacity breaths, a calculated apnea period of about 6 minutes could be tolerated. It should be noted that after denitrogenation, in a patient with a patent airway, apneic oxygenation will supply adequate oxygen for much longer periods of apnea (17).

Until recently, anesthetists have thought in terms of "preoxygenation." Due to the limited information obtained from arterial oxygen saturation or content, a change in focus from "preoxygenation" to the more relevant concept of "denitrogenation" should be made. Complete denitrogenation can be especially important in clinical situations of difficult intubation, or of decreased functional residual capacity (obesity, ascites, pregnancy), and in situations where oxygen saturation is critical (coronary artery disease, increased intracranial pressure, anemia, sickle cell disease) (17).

In addition to current monitoring practices, mass spectrometry, either with central or stand alone units, has proven to be clinically valuable. This study demonstrates one further use of mass spectrometry in the clinical setting; it allows the accurate tracking of nitrogen washout (or oxygen washin) during "preoxygenation." Such quantitative information on the adequacy of preoxygenation is not available through any of the other standard anesthetic monitors because one must measure either end-tidal nitrogen or end-tidal oxygen to determine the adequacy of the denitrogenation in patients irrespective of oxygen saturation.

In patients with pulmonary disease or over 44 years of age, the closing capacity begins to encroach on functional residual capacity (FRC) (17). With tidal volume breathing, there may not be communication between ambient oxygen and some of the terminal airways throughout the respiratory cycle. Indeed, some areas of the lung may not be denitrogenated during tidal breathing. Under those circumstances end-tidal nitrogen values may be spuriously low because they do not represent dilution of the total lung volume. In this type of patient, inspiratory capacity breathing would be of greater benefit because it would open more lung units and allow for more complete denitrogenation.

In conclusion, in ASA physical status I individuals, 3 minutes of tidal breathing reduces end-tidal nitrogen to approximately 1% and provides a more complete washout of nitrogen from the lungs than do four inspiratory capacity or vital capacity breaths. Equivalent nitrogen washout from the lungs to an end-tidal nitrogen of approximately 6% is achieved by preoxygenation with 100% oxygen for 2 minutes of tidal breathing, with eight inspiratory capacity breaths or four vital capacity breaths. In healthy subjects, end-tidal nitrogen provides a useful monitor of the completeness of denitrogenation and, therefore, the adequacy of the process we have called preoxygenation. We recommend a change in focus from "preoxygenation" to "denitrogenation."

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Epidural Anesthesia for Patients with Amyotrophic Lateral Sclerosis

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Key Words: COMPLICATIONS, AMYOTROPHIC LATERAL SCLEROSIS. ANESTHETIC TECHNIQUES, EPIDURAL.

Amyotrophic lateral sclerosis (ALS) is characterized by pathologic degeneration of the lower motor neurons, motor nuclei of the caudal brainstem, and the descending pathways of the upper motor neurons. Progressive muscular atrophy and bulbar palsy with fasciculations are its clinical manifestations.

Atrophy and weakness of respiratory muscles eventually lead to respiratory failure and death. The impairment of respiratory function, together with the weakened upper airway muscles, may affect anesthetic management. The response to muscle relaxants, either depolarizing or nondepolarizing, is also altered in ALS. Patients with ALS require special care throughout the perioperative period.

The following case reports illustrate the safety and usefulness of epidural anesthesia in patients with ALS.

Report of Three Cases

Case 1

The patient was a 52-year-old, 36-kg woman with an 8-year history of ALS, who was scheduled for supravaginal hysterectomy for leiomyoma of the uterus. She had three episodes of hemorrhagic shock 4 months previously due to massive bleeding from the leiomyoma. Preoperative evaluation revealed a thin middle-aged woman with severe bulbar palsy, flaccid upper extremities, and lower limb muscle weakness. She had difficulty in speaking and swallowing and was fed through a nasogastric tube. Blood pressure was 122/78 mm Hg, pulse rate was 86 beats/minute, and respiratory rate was 22 breaths/min. No abnormalities were found on examination of the heart and lungs. The patient could not perform pulmonary function tests because of weak oropharyngeal muscles. Arterial blood pH was 7.44, PO_2 was 91 mm Hg, and PCO_2 was 44 mm Hg while breathing room air. Chest x-ray study showed no abnormalities.

Preanesthetic medication consisted of intramuscular atropine (0.5 mg) and diazepam (10 mg). Forty minutes later, an epidural catheter was inserted through the third lumbar vertebral interspace while the patient was in the right decubitus position. After the catheter was taped to the skin, the patient was returned to the supine position. A test dose of 2 ml of 2% lidocaine was injected through the epidural catheter. The patient was hemodynamically stable. Five minutes later, an additional 8 ml of 2% lidocaine was injected through the catheter. The level of anesthesia as determined by pinprick 15 minutes later extended to T6. The patient was given a humidified mixture of air and oxygen (35% O_2) through a face mask, and experienced no respiratory discomfort in either the supine or lithotomy position. Monitoring included continuous electrocardiogram (ECG), blood pressure, pulse oxymetry, and rectal temperature. Additional increments of 2% lidocaine (7 ml) were administered over the ensuing 1.5 hours to maintain satisfactory analgesia. The intraoperative course was uneventful (blood pressure ranged 86 to 130/42 to 80 mm Hg, heart rate 90 to 110 beats/minute without arrythmias throughout). Arterial pH remained at approximately 7.39, PO_2 at 160 mm Hg, and PCO_2 at 42 mm Hg during surgery. Blood loss amounted to 150 ml, and 850 ml of lactated Ringer's solution was given. Morphine sulphate (2 mg in 10 ml saline solution) was injected through the epidural catheter at the conclusion of surgery. This successfully controlled incisional pain without complications, including respiratory depression. Recovery of motor function of the lower

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extremities to the preoperative level was completed within 2 hours postoperatively.

Case 2

The patient was a 67-year-old, 59-kg man with prostatic hypertrophy scheduled for suprapubic prostatectomy. At the age of 66 years, weakness of lower legs developed and the diagnosis of ALS was made. Preoperative evaluation revealed moderate muscle atrophy and weakness, with fasciculations in upper and lower extremities. Mild bulbar palsy and difficulty in speaking were also noted. Pulmonary function tests showed a forced vital capacity (FVC) of 67% of predicted and a $FEV_{1.0}$ of 78% of predicted value. Arterial pH was 7.42, PO_2 was 78 mm Hg, and PCO_2 43 mm Hg while breathing room air. An electrocardiogram revealed incomplete right bundle branch block. The chest was clear on auscultation.

Preanesthetic medication consisted of 10 mg of diazepam and 0.5 mg of atropine, intramuscularly. Thirty minutes later, a catheter was inserted through the third lumbar vertebral interspace. Lidocaine (2 ml of 2%) was injected as a test dose, followed by an additional 8 ml. After 15 minutes, decreased sensation to pinprick was apparent to T6 bilaterally. Ephedrine (20 mg) was administered intramuscularly to prevent hypotension. Oxygen was administered through a nasal cannula at a flow rate of 2 liters/minute. Intraoperatively, blood pressure ranged between 90 to 110/56 to 74 mm Hg, and pulse rate between 70 and 86 beats/min throughout. Additional increments of 2% lidocaine (7 ml) were administered over the ensuing 2.5 hours to maintain satisfactory analgesia. Morphine sulphate (2 mg in 10 ml saline solution) was injected through the epidural catheter 20 minutes after completion of surgery for postoperative pain relief. The postoperative course was uneventful, and the patient felt almost no incisional pain.

Case 3

The patient was a 56-year-old man, weighing 53 kg, with prostatic cancer, who was scheduled for transurethral resection of the prostate. Past medical history was significant for a gastrectomy because of a gastric polyp performed 4 years previously. Two years before the admission described here, the patient had undergone orchidectomy under spinal anesthesia. The patient had fasciculations and atrophy of lower legs for 4 months, and the diagnosis of ALS was made 2 months before the operation. Preoperative evaluation revealed mild muscle atrophy and weakness in the lower extremities. Pulmonary function studies showed a FVC 81% of the predicted value and a $FEV_{1.0}$ of 55% of the predicted value. Blood pressure was 116/74 mm Hg, pulse rate 70 beats/minute, and respiratory rate 18 breaths/minute. No abnormalities were found on physical examination of the heart and lungs. While breathing room air, arterial pH was 7.45, PO_2 was 87 mm Hg, and PCO_2 was 39 mm Hg. Chest x-ray study showed no abnormalities. Preanesthetic medication consisted of intramuscular atropine (0.5 mg). Fifteen minutes later, an epidural catheter was inserted through the fifth lumbar vertebral interspace with the patient in the sitting position. Lidocaine (2 ml of 2% as a test dose, followed by an additional 15 ml) was injected through the epidural catheter. After 10 minutes, decreased sensation to pinprick was apparent to the T8 dermatomal level bilaterally. Oxygen, at 6 liters/minute, was administered through a face mask. Intraoperatively, blood pressure ranged between 84 to 124/46 to 70 mm Hg and pulse rate from 70 to 90 beats/minute throughout. Additional increments of 2% lidocaine (10 ml) were administered over the ensuing 2 hours. During surgery, the arterial pH remained at about 7.46, PO_2 at 355 mm Hg, and the PCO_2 at 43 mm Hg. The postoperative course was uneventful, and there was no exacerbation of neurologic signs or symptoms.

Discussion

Patients with ALS often have disturbances in swallowing as a result of weakened pharyngeal muscles. Thus, it is reasonable to assume that these patients are susceptible to silent regurgitation and upper airway obstruction. Nishino et al. (1,2) found that general anesthetics and hypoxia depress the swallowing reflex in a dose-related manner, which also could, in turn, increase the risk of regurgitation and upper airway obstruction in these patients. In addition, of course, most general anesthetics depress ventilation through direct action on the respiratory center, chemoreceptors, and/or respiratory muscles. Thus, the use of respiratory depressants should be carefully titrated or avoided if possible in patients with ALS.

The possibility of a sudden increase in plasma potassium levels and possible resultant ventricular arrhythmias or fibrillation after the administration of succinylcholine in patients with neuromuscular disease and lower motor neuron disease has also been reported by several investigators (3–5) and, thus, we did not use succinylcholine. Furthermore, patients with ALS frequently are highly sensitive to nondepolarizing muscle relaxants, as are patients with myasthenia gravis (6,7). While taking into account the above disadvantages of general anesthesia with muscle relaxants in patients with ALS, we decided to use lumbar epidural anesthesia for these three cases because the surgical procedures were confined to the lower abdomen and genital area. It should be noted, however, that lumbar epidural anesthesia could also exert ventilatory impairment if the level of sensory block goes above T6 because this level can lead to a decrease in the expiratory reserve volume (8). Such an adverse effect can result in the inability to cough effectively, leading to a reduced clearance of secretions from the airway. Fortunately, the highest hypalgesic segment in these cases was T6 and, consequently, arterial blood gas tensions remained normal intraoperatively.

Excerbation of pre-existing neurologic damage after spinal and epidural anesthesia has been described by Kane (9) and Vandam and Dripps (10). However, most of the reported cases were related to coexisting lumbar disc hernia, spinal tumor, or technical problems. The latter should be extremely rare if the procedure is performed by highly trained staff. Furthermore, to our knowledge, there are no data describing deterioration of neurologic function in patients with degenerative disease of the spinal cord after epidural anesthesia. This does not mean that the epidural anesthesia is invariably safe for patients with ALS, but we believe that the risk of general anesthesia with muscle relaxant is greater than that of a well-managed epidural anesthesia in this group of patients. General anesthesia with tracheal intubation might assure adequate intraoperative ventilatory management, but it could also increase the risk of aspiration, airway obstruction, and the need for postoperative artificial ventilatory support. Finally, regardless of the type of anesthesia used, the possibility, however remote, of postoperative deterioration of the neurologic status of patients should always be mentioned to patients with ALS.

We conclude that the epidural anesthesia is a safe and useful method to manage patients with ALS undergoing lower abdominal or lower extremity surgery.

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Letters to the Editor

Concentrations of Morphine in the Cerebrospinal Fluid after Femoral Perineural Morphine Administration

To the Editor:

Mays et al. have, in their controlled study of local analgesia without anesthesia following perineural injections of morphine (1), attributed the good results of perineural morphine administration in patients with chronic pain in part to axonal uptake and transport of morphine to the spinal cord. Other clinical studies (2, 3) of analgesia associated with perineural administration of morphine in postoperative patients have failed to demonstrate a analgesic effect of this method of administration.

In a preliminary attempt to test the hypothesis of an axonal opiate transport, we have on two occasions measured the spinal fluid morphine concentrations after the perineural injection of morphine about the femoral nerve.

In two patients, 55 and 75 years of age, scheduled for hip surgery we preoperatively inserted a 16 G catheter in the femoral neuro-vascular sheath. One hour before surgery, performed under spinal analgesia with bupivacain, morphine 8 mg in 20 ml of isotonic NaCl was injected through the femoral catheter. Plasma morphine concentrations were then measured with a radioimunoassay technic (4) 0, 30, 60 and 90 min after the morphine was given. Spinal fluid morphine concentration was also measured, once in each patient, 60 min in one and 90 min in the other after the perineural injection.

In Table 1 are listed the resulting values of plasma and spinal fluid morphine concentrations. One of the patients had received nicomorphine 5 mg 8 hours earlier, this accounting for the morphine plasma concentration at 0 min. The catheters, as confirmed radiographically, were placed high in the lumbar plexus, about 8–10 cm from the epidural space.

The doses we gave were large and the time elapsed before spinal fluid samples were taken for analysis was well within the time reported necessary to obtain clinical effects in the study of Mayes et al (1).

The morphine concentrations obtained in the spinal fluid found in our two patients are of the same magnitude as would have been expected after intramuscular injection (5).

Table 1. Plasma and CSF morphine concentrations after perineural administration of 8 mg of morphine

Time after administration (min)	Morphine concentrations (ng/ml)			
	patient 1		patient 2	
	plasma	CSF	plasma	CSF
0	1.4		0	
30	26		38	
60	23	2.7	30	
90	19		26	2.8

Direct spread of morphine injected into a peripheral neurovascular sheath, such as that investing the femoral nerve centrally to the lumbar roots, from there to the epidural space and from the epidural space to the CSF in concentrations adequate to produce analgesia by acting directly on the spinal cord appears unlikely on the basis of the present preliminary findings.

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What Wisdom is There in Administering Elective General Anesthesia to Children with Active Upper Respiratory Tract Infection?

To the Editor:

While the recent paper of Tait et al (1) has some basic science interest with regards to the effects of anesthetic gases on viral virulence in ferrets, I must take issue with their suggestion that elective general anesthesia administered to children with active upper respiratory tract infections (URI) is a safe practice.

Most URIs in children are associated with rhinovirus, adenovirus or respiratory syncytial virus (2), yet Tait, et al utilized type A influenza virus. The difference between viral pathogens is an important distinction since typical URI viral pathogens do not readily infect lower airways, whereas the influenza virus is associated with lower airway disease and thereby increased morbidity (2), and indeed some of the ferrets developed evidence of pneumonia. One could argue that the pneumonia was acquired secondary to the decreased respiratory mechanics and depressed ciliary motility during the anesthetic exposure and that a larger experimental group ($n > 9$) may have resulted in findings of increased morbidity associated with general anesthesia. It is also unclear from their paper how many of the nine experimental animals received diethyl ether, halothane or enflurane. Needless to say, diethyl ether has no pertinence to modern clinical anesthesia practice. Their ferret population was exposed to 1 MAC concentrations for one hour but it should be remembered that there was no surgical stimulation (i.e., stress), no airway management (i.e., facemask or endotracheal tube), no positive pressure ventilation and no additional anesthetic drugs administered (i.e., N_2O, muscle relaxants, barbiturates, etc.). Without taking into account all of these associated clinical factors it is unsafe to draw the conclusion that anesthesiologists are unnecessarily postponing surgery.

Even Tait and Knight's (3) paper published in 1987 investigating the effects of general anesthesia on URIs in children does not convince me that this is a safe practice. In this paper (3) they imply that, because 78 children (with symptomatic URIs), who had 19 minutes of halothane/N_2O/O_2 anesthesia, had 1 less day of sore throat, 3 less days of malaise and less sneezing and congestion, that this was the result of halothane inhibition of viral replication. In the papers they cited to support the anti-viral properties of anesthetics it is interesting to note that none of these studies used URI viral pathogens, but concentrated on measles virus, herpes simplex virus and various of animal viruses (4–7). It should also be noted that in these studies (4–7) the anesthetic exposure time was measured in days and first effects were seen at 12 hours, clearly out of the range of most clinical anesthetic durations.

As a clinician involved with administering general anesthesia to children it is clear to me that once one anesthetizes enough children with URIs one will begin to see increased morbidity. The heightened airway reflexes, increased secretions leading to atelectasis and/or endotracheal tube obstruction, intraoperative fevers and postoperative hypoxemia are far more serious perioperative complications than shortening the duration of the innocent symptoms associated with URIs in healthy children. Liu, et al (8) for example, have data showing a significantly higher incidence of critical incidents occurring in infants with URIs undergoing anesthesia. More studies like that by Liu et al will allow us to educate our surgical colleagues and concerned parents about the wisdom of conducting general anesthesia on an elective basis in children coming for surgery.

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In Response:

We are grateful for the opportunity to respond to Dr. Hinkle's comments regarding our recent article.

The decision whether or not to proceed with anesthesia for the patient who presents with an upper respiratory tract infection (URI) has been an enduring clinical dilemma. Until recently, this problem has been addressed only by empirical observation. Although information obtained in this way is useful in pointing out potential problems, it does nothing to determine incidence or cause and effect. We have therefore designed a series of studies in an attempt to evaluate, in a controlled manner, the interaction between anesthesia and the infectious process, at both the clinical and the basic science levels.

Our recently published article involving ferrets represents a basic science approach to this issue. The purpose of this study was to evaluate the histopathologic response to influenza virus infections in ferrets using different anesthetic agents. Although we are sensitive to the potential clinical relevance of the results in terms of the histopathology, we in no way mean to imply that results obtained from studying ferrets should alter the clinical management of the infected patient.

In response to Dr. Hinkle's specific comments regarding our ferret study, we concur that most URIs seen in clinical practice do not involve influenza virus. Influenza is important as a human pathogen, however, in that it has a strong propensity to occur in epidemics. Influenza virus was chosen because it has been thoroughly investigated in ferrets with respect to symptomatology and histopathology. As the primary purpose of this study was to examine the effect of different anesthetic agents on histopathology and course of infection, influenza virus was an appropriate choice. Also, the pattern of influenza infection in the ferret closely parallels that observed in man, i.e., the infection is localized primarily in the upper respiratory tract and is characterized by a similar symptom complex, which made selection of the virus that much more attractive.

While it is true that a mild, patchy pneumonia was observed in some of the infected animals, as we stated in the paper this observation was apparent in both anesthetized and non-anesthetized animals. Dr. Hinkle's suggestion that the pneumonia observed in this study was secondary to the anesthetic depression of ciliary motility is therefore purely speculative. With respect to the number of infected animals receiving each anesthetic agent, nine received diethyl ether, nine received halothane, and nine were anesthetized with enflurane. We agree that the ferrets had no extrinsic stimulation, but our purpose was not to simulate the clinical situation, rather to evaluate the anesthetic effect alone on the histopathologic response to the virus.

With respect to our clinical study published in 1987[1], which is much more relevant to the question of patient safety, Dr. Hinkle has taken our conclusions completely out of context. We do not advocate the widespread administration of anesthesia to patients harboring acute URIs, as Dr. Hinkle implies, and we never have. Our suggestion that it may be unnecessary to postpone surgery due to the presence of an URI is restricted to a finite population: patients who are scheduled for minor surgical procedures in which the trachea is not intubated (e.g., myringotomy) and who present with a mild, uncomplicated URI. We are quite aware that there are many situations in which anesthesia is contraindicated in patients with acute viral infections and therefore we have deliberately avoided extrapolating our data to a more general population.

Specifically, in this study we determined that there was no increase in risk of perioperative complications (laryngospasm, postoperative pneumonia, etc.) for children aged 1–12 years presenting for myringotomy and tube placement without tracheal intubation while harboring uncomplicated URIs. We further observed that the postoperative course defined by symptom prevalence and duration was less for the group of symptomatic children following anesthesia and surgery than it was for a matched group of symptomatic controls who did not have anesthesia and surgery. Dr. Hinkle presents some of this postoperative data but fails to include that the prevalence of sore throat, sneezing, malaise, fever, and productive cough was also significantly less in the group following anesthesia. In this paper we cited some of our *in vitro* work which shows that anesthetic agents can reversibly inhibit the replication of certain viruses in a dose dependent fashion. Although a cause-effect relationship between anesthesia and the observed amelioration of symptoms could not be established due to the potential confounding effects of the surgery, these *in vitro* studies demonstrate a strong sensitivity of certain viruses to the volatile agents, and thus provide a possible explanation of our clinical findings. As Dr. Hinkle correctly points out, we have not studied the effects of anesthetics on the respiratory viruses *per se,* although this is now underway. We would remind him, however, that parainfluenza virus, a common causative agent of URI, belongs to the *paramyxoviridae,* as do measles and Sendai virus, and may therefore be expected to respond in a similar manner.

Finally, Dr. Hinkle cites the work of Liu, et. al., (2) presented recently as an abstract at the World Congress. While it is true that Dr. Liu did observe a significant number of "critical incidents" on induction among infants with URIs, he and his co-workers also reported no increase in morbidity and mortality among symptomatic children. Because we did not study infants nor intubated children, one cannot compare our results to theirs. We are therefore somewhat bemused by Dr. Hinkle's suggestion that there is a need for "more studies like Liu's, et. al." Does this imply that studies which do not agree with one's own preconceived ideas should not be pursued?

Our clinical study took five years to complete. We believe it is based on sound epidemiological principles. While we welcome the contributions of other authors, like Dr. Liu, to help solve this perennial problem, we stand by our results. Our studies are not designed to dispute dogma, but to help the anesthesiologist better understand the interactions between anesthesia, surgery, and the infectious process, and to suggest the advantages of a scientific, rather than a purely empirical basis for decision making.

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Emergency Airway Management in Trauma Patients with a Suspected Cervical Spine Injury

To the Editor:

We would like to comment on the description by Grande, et al (1) of emergency airway management in patients with a suspected cervical spine injury (SCI). Grande, et al cite the American College of Surgeons publication on Advanced Trauma Life Support (ATLS) (2) in suggesting that "Oral intubation with a standard laryngoscope and manual in-line traction (MIAT), also referred to as manual C-spine immobilization . . ." be the predominant method of tracheal intubation should this be emergently required in patients with SCI. (1) They also state that nasal intubation of these patients is fraught with difficulty and should be avoided. We would like to address some of the statements, and hopefully add to the understanding of airway management possibilities in these patients.

Although the ATLS manual does recommend "in-line traction" when oral laryngoscopy is performed in patients with SCI, the term "traction" may have a potentially dangerous connotation. No study has definitively addressed the issue of C-spine movement with any method intubation in trauma patients, and none has addressed the neurologic consequences of this movement. However, Bivins, et al (3) were able to document significant osseous distraction in recently deceased trauma patients with known cervical injuries when a traction method of immobilization was employed. These results suggest that the potential for aggravating certain cervical spine injuries does exist when "traction" is used for immobilization. Until more data are available, the most prudent approach is for those responsible for airway management in the presence of SCI to ensure that the head and C-spine are kept as still as possible during laryngoscopy, avoiding the use of an external force in any single plane or direction.

Grande, et al also state that nasal intubation ". . . should not be performed in frightened, inebriated, obtunded, and comatose patients . . ." because of the potential for exacerbation of an underlying cervical injury due to patient thrashing. We know of no study to suggest that oral laryngoscopy in these same patients, without sedation or local anesthesia, is better tolerated and less ready to cause patient movement. It is further suggested by Grande, et al that the risk of postoperative sepsis due to sinusitis as a result of nasal intubation should mitigate against the use of this technique in patients with SCI. The data on this topic indicate that the risk of postoperative sinusitis is a function of duration of intubation, which often correlates with the amount of neurologic insult suffered. (4) The possibility for infection after prolonged nasal intubation is a more appropriate concern in the intensive care unit, and should not preclude the short term use of this method of airway management in emergency department patients with SCI.

Aside from blind nasal intubation or direct oral intubation after laryngoscopy, the management options for airway control in trauma patients include other techniques worthy of mention that are not discussed by Grande, et al. Orotracheal intubation employing the transillumination technique with the use of a lighted stylet can rapidly provide an airway in comatose, obtunded, or sedated patients. (5,6) This technique is safe and rapid in apneic paralyzed subjects. (7) Similarly, research is currently underway on use of a flexible lighted stylet in nasotracheal intubation. This may allow more rapid intubation through the nares in apneic or near-apneic subjects. Tactile intubation, another option for tracheal intubation in comatose trauma patients, can be performed in subjects while maintaining cervical immobilization. (8) All of these techniques are promising, but in need of research to define their safety in patients with SCI, particularly with regard to cervical spine motion during intubation. Transtracheal jet ventilation and cricothyroidotomy should not be forgotten in patients with a high likelihood of SCI, especially if tracheal intubation is difficult or unsuccessful. (9) These can be performed without gross C-spine manipulation.

It is unlikely that one method of tracheal intubation alone will satisfy the airway needs of all traumatized patients at all centers in emergency situations. Until then, common sense and proficiency in a few options can assist the airway physician in these cases.

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In Response:

Yealy et al raise several points of discussion regarding our original communication (1), to which we respond individually. Primarily, it must be remembered that our original comments were in response to an earlier communication by Gorback (2) and were not intended to be a complete treatise on airway management of the trauma patient.

In our original communication, the technique for cervical stabilization during oral intubation with a standard laryngoscope was called "manual in-line axial traction" (MIAT). Presently, the terms "traction" and "immobilization" are sometimes incorrectly used interchangeably when referring to *stabilization* of suspected cervical spine injury. As Yealy et al mention, there is literature to show that "the potential for aggravating certain cervical spine injuries does exist when 'traction' is used for immobilization" (note the misuse of terms in this sentence). Yet, it has also been demonstrated that traction is helpful in the management of other cervical spine injuries (3). Ultimately, the goal of these manual manuevers is to stabilize the spine and thus prevent further injury. We are unaware of any report that describes the ideal amount of force to be used when applying traction, even if that force should equal zero. It is equally important that the force be applied in the correct plane, relative to a particular injury. In any case, it is probably impossible to make a general statement of how much traction should be applied, unless feedback information is available (e.g., from fluoroscopy). Ideally, a neurosurgeon should be present for immediate consultation and guidance.

In the study by Bivins et al, a uniform traction force of 6.8 kg was applied irrespective of the particular injury (4). Those authors list the following limitations of their study: 1) the effects of different traction weights on the unstable cervical spine during orotracheal intubation were not addressed, 2) the force required to visualize the vocal cords (i.e., laryngoscopy) was not measured or standardized, and 3) all radiographs were taken with weights applied to the arms, which may have caused the documented abnormalities. Further, to use the findings of one study in which deceased patients (who no longer have protective cervical muscle spasm) demonstrated fracture destabilization as a basis for general methods of practice may be cavalier. Furthermore, patients, such as those studied by Bivins et al, who suffer such devastating blunt trauma as to fail resuscitation may not be representative of salvageable trauma patients.

For these reasons, we assume a more moderate position. While agreeing with Yealy et al, that in certain instances traction per se may be deleterious, we recognize that in some cases it is beneficial and thus warranted. Again, there presently is no clinically feasible method available to guide the application of traction force. Therefore, it is difficult to make any recommendations other than to stabilize the injury. Stabilization often may involve a dynamic interplay between traction and immobilization such that an ideal amount of force is applied against the force generated by the intubator.

The second point raised by Yealy et al relates to the negative aspects of nasal intubation when compared with oral intubation of trauma patients with cervical spine injury. Yealy et al refer to the use of oral intubation "in patients with no sedation or local anesthesia." In our original correspondence general statements were made and we did not describe specific preparations for patients about to undergo intubation. Obviously, pharmacologic agents are used judiciously to optimally prepare the patient for the intubation. In most cases at our center, this includes an appropriate combination of analgesic, sedative, hypnotic, and muscle relaxant, as the situation dictates.

One basic, immediate concern that Yealy et al neglected to mention is that, in trauma patients with cervical spine injury, one must consider the possibility of associated head injury and cribriform plate fracture. Nasal intubation is contraindicated in these circumstances because violation of the cranial vault by tubular devices is a well-documented complication (5). Although the possibility of postoperative sepsis as a result of nasal intubation should not be overemphasized in short-term airway management, it must not be forgotten. A large proportion of seriously injured patients require extended postoperative ventilatory support. To prevent further compromise secondary to infection, which can be disastrous in this type of patient, nasally intubated trauma patients usually undergo secondary oral intubation or tracheostomy. Experienced "airway physicians" (6) working in high-volume trauma centers often rely upon their clinical judgement and resort to initial oral intubations or surgical airways to preclude a second procedure, which will carry its own associated risks. These second procedures can often be precarious such as when the trauma patients develop complications such as massive cervical edema or when they are maintained in a cumbersome apparatus such as a halo vest.

In a study performed by emergency medicine physicians comparing oral and nasal intubation in unconscious drug-intoxicated patients, it was concluded that oral intubation was preferable (7). In that study, oral intubation had a greater success rate (100% oral vs. 65% nasal), was quicker (64 seconds for oral vs. 276 seconds for nasal), needed fewer attempts (1.3 per patient for oral vs. 3.7 per patient for nasal), and had drastically fewer complications (0% for oral vs. 69% for nasal).

Other management options for airway control in trauma patients were alluded to in our original communication and are well summarized elsewhere (8). Intubation using transillumination with flexible lighted stylets and tactile intubation can be useful, efficacious methods, albeit they appear to be more popular with emergency medicine physicians. Of course, with any trauma patient, one must be prepared to resort to one of the surgical airway techniques (cricothyroidotomy, transtracheal jet ventilation, tracheostomy) if necessary.

In closing, we reiterate that one of the ultimate goals in airway management of trauma patients with spinal injury is to prevent further injury through *stabilization*, which may include traction or immobilization, as the particular injury and circumstances dictate. Finally, we caution against issuing any general "blanket" statements regarding medical matters, especially when they concern the management of trauma patients.

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Recurrent HSVL and the Use of Epidural Morphine in Obstetrics

To the Editor:

Crone et al. (1) confirmed the link between reactivation of herpes simplex virus labialis (HSVL) infection and use of epidural morphine in obstetric patients, although they reported a lower incidence than we found (2). The difference in incidence might be explained by the lower total dosage of epidural morphine used by Crone et al. They administered a single 4-5 mg epidural dose of morphine, while in our study 3-5 mg morphine was given up to twice a day for an average of 2.3 days.

In their discussion, however, Crone et al. state that an altered immunologic response is unlikely to be involved as a reactivating mechanism because obstetric patients who underwent a cesarean section without epidural morphine did not reactivate HSVL (1). However, we think the occurrence of HSVL in obstetric patients given epidural morphine, represents a multifactorial phenomenon in which depressed cell mediated immunity (CMI) might play a role. Certainly defence mechanisms against herpes simplex infections are mediated through CMI (3–4) and pregnancy is associated with depression of some aspects of CMI (3–7).

We agree that the difference in incidence of HSVL reactivation in obstetric patients is related to whether or not they had received the epidural morphine. But more factors play a role. For example, we followed 32 women having hysterectomies in whom there was no reason to assume a depressed CMI. They were given epidural morphine for postoperative pain relief. Only 1 of the 32 developed HSVL, whereas 15 developed itching (8). Nonobstetrical patients given epidural morphine for postoperative analgesia after abdominal or gynecologic procedures rarely developed HSVL.

Alterations in CMI are definitely not the only cause for reactivation of HSVL in obstetric patients. Indeed, obstetrical patients not receiving epidural morphine rarely develop HSVL even though their pregnancies have altered their CMI. With depressed CMI, a triggering factor such as mechanical irritation from rubbing and scratching the skin in response to itching may, however, cause reactivation of HSVL. That patients given epidural morphine after cesarean section develop reactivation of HSVL more frequently than patients given epidural morphine after a hysterectomy may be related to CMI depression associated with pregnancy. But different levels of steroid hormones or certain proteins that could be responsible for the depression of CMI, also might have more direct influence on the reactivation of HSVL in the obstetric patients (3–4).

We believe that many factors need to be considered in order to explain why reactivation of HSVL is restricted almost entirely to obstetric patients and especially those given epidural morphine. Further studies are needed to clarify this relationship.

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Spinal Anesthesia in Children: Surface Anatomy

To the Editor:

Spinal anesthesia can be safely and reliably performed in high risk infants (1,2). However, lumbar puncture must be performed below the third lumbar vertebra (1) to avoid possible damage to the spinal cord, which extends further caudad in small children. The iliac crests are commonly used as landmarks for determining the position of lumbar vertebrae and intervertebral spaces when spinal or lumbar epidural anesthesia is to be performed (3). In adults, the line drawn between the highest point of the iliac crests is said to cross the midline at the level of the fourth lumbar vertebra (4) or the L3-4 interspace (5).

However, the preceding does not hold true for neonates, in whom the pelvis is proportionately smaller than in adults for several years after birth. The secondary ossification center for the iliac crest does not appear until puberty (5) and the sacrum, which makes up a large segment of the pelvic girdle in children, is situated higher in relation to the iliac crests than in adults (6). This means the intercristal line is unlikely to cross the midline at the same level as in adults. The surface anatomy of relevance to spinal anesthesia in neonates and small children has not, however, been described. We, therefore, examined 500 lateral and anteroposterior radiographs of the lumbar spine in children aged one day to 16.3 years. From these data we find that, on average, the intercristal line crosses the midline at the level of the fifth lumbar vertebra in children, and even lower, at the L5-S1 interspace, in neonates.

We therefore conclude that the intervertebral space below the intercristal line can be safely used in performing spinal anesthesia in neonates, since traumatic injuries of spinal cord, which is located much higher, are unlikely.

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Volume Replacement in the Patient with Limited Venous Access

To the Editor:

Placement of central venous lines for both perioperative monitoring and rapid administration of blood and fluids is a standard practice in managing patients undergoing major transplant surgery (i.e. orthotopic heart or liver transplant). Often the anesthesiologist is confronted with grossly altered and/or limited venous access that makes line placement extremely difficult.

We recently managed a patient for orthotopic liver transplant who previously had multiple operations with many of the major venous access sites now unavailable. Since the operative site in this particular patient mandated that fluid and volume replacement not be returned to the heart by the inferior vena cava, we inserted all our volume replacement and monitoring lines in major central veins draining into the superior vena cava.

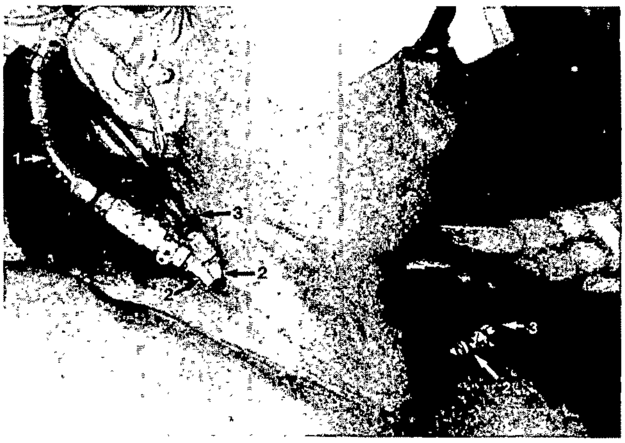

Figure 1. Patient prior to surgery with Swan-Ganz® catheter (1) placed in 7.5 French sheath (2) and rapid infusion pump (3) attached to separately placed 7.5 French sheaths.

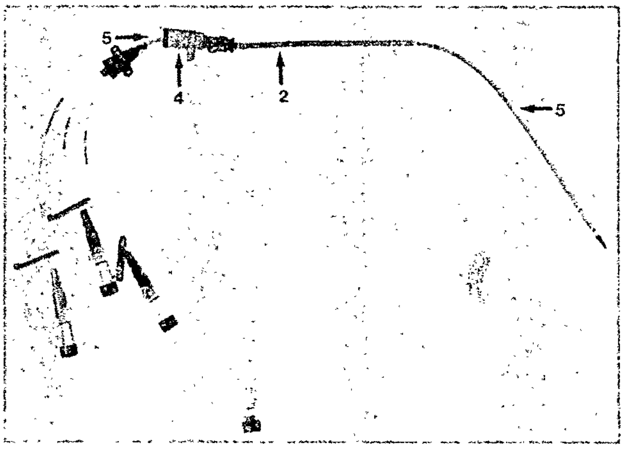

Figure 2. 7.5 French sheath (2) with diaphragm (4) attached and triple lumen catheter (5) passed through the diaphragm.

The approach we have developed to resolve this problem is to perform internal jugular cannulation using the standard Seldinger technique following venipuncture. After the J wire is placed, the catheter and dilator are not advanced; instead, a second separate internal jugular puncture is made and a second J wire is positioned. Following positioning of both J wires, the dilator and sheath are then advanced as usual. After placing the sterile sheath over the Swan-Ganz® catheter and placing the diaphragm on the 7.5 French catheter the Swan-Ganz® catheter can be floated into position. The rapid infusion pump can be connected to the second 7.5 French sheath as shown in Figure 1. If one does not require a rapid infusion pump, the diaphragm used for passing a Swan-Ganz® catheter can be placed on the 7.5 French catheter and a triple lumen catheter can be passed through the diaphragm (Figure 2). This provides 3 additional venous ports. If further venous access is required an additional subclavian or internal jugular catheter can be placed using the Seldinger technique.

We have found it necessary to utilize this technique in five of our 180 liver transplantation patients. We have had no complications associated with this technique. We do not recommend routine placement of two central lines in such close proximity to each other in the same major central vein. We merely describe a solution to a clinically challenging problem.

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New and Old Methods for Calculation of Ventilatory Deadspace

To the Editor:

In 1986 we published a paper on gas exchange during controlled ventilation in children with congenital heart disease (1). The study was performed using the single breath test for CO_2 (SBT-CO_2) obtained "on-line" with the aid of a computer. SBT-CO_2, when combined with arterial blood sampling, allows calculation of the physiological deadspace fraction V_Dphys/V_T.

$$\frac{V_Dphys}{V_T} = \frac{FaCO_2 - F_{\bar{E}}CO_2}{FaCO_2 - F_ICO_2} \qquad (1)$$

where $FaCO_2$ is the FCO_2 of a gas in equilibrium with arterial blood, and F_ICO_2 is the inspiratory FCO_2. The alveolar deadspace fraction V_Dalv/V_Talv is obtained from:

$$\frac{V_Dphys - V_Daw}{V_T - V_Daw}, \qquad (2)$$

where V_Daw is the airway deadspace.

Recently, we reviewed our methodology, and this has led us to modify our deadspace estimates. The changes hinge on the phenomenon of rebreathing in the limbs of the Y-piece. Part of the expired CO_2 which is registered in the analyzer returns to the patient in the initial part of the next inspirate (2). This rebreathing would appear to be unavoidable unless one-way valves (which are not acceptable in clinical practice) are used. Thus the volume of CO_2 (V_TCO_2) registered per single breath test is greater than the volume of CO_2 that is in fact eliminated; a greater volume than would be collected in a Douglas bag. In our deadspace estimates we subtracted this rebreathed volume from the registered V_TCO_2 and thus calculated deadspace variables in order to give the same values as would be obtained using a Douglas bag. Mixed expired FCO_2 ($F_{\bar{E}}CO_2$) was estimated from V_TCO_2/tidal volume in this way, and was substituted in the deadspace in equation 1. F_ICO_2 is regarded as zero (as would be the case in a conventional Douglas bag experiment). In effect, this method of calculation attributes the apparatus deadspace associated with the rebreathing to the patient. Consequently, V_Dphys and V_Dalv are overestimated.

Table 1. Comparisons of New and Old Methods for Calculation of Ventilatory Deadspace

Circulation	V_Dphys/V_T old	V_Dphys/V_T new	V_Dalv/V_Talv old	V_Dalv/V_Talv new
Normal	0.24 ± 0.05	0.20 ± 0.05 (0.20 ± 0.05)	0.10 ± 0.03	0.05 ± 0.03 (0.05 ± 0.03)
Left-right shunts	0.28 ± 0.06	0.21 ± 0.06 (0.21 ± 0.06)	0.13 ± 0.06	0.05 ± 0.05 (0.05 ± 0.05)
Right-left shunts	0.41 ± 0.11	0.37 ± 0.10 (0.35 ± 0.10)	0.30 ± 0.12	0.25 ± 0.11 (0.22 ± 0.12)
Mixed shunts	0.33 ± 0.008	0.25 ± 0.08 (0.26 ± 0.09)	(0.20 ± 0.08)	0.12 ± 0.07 (0.12 ± 0.08)

The revised method of calculation is intended to avoid this problem of overestimation, even though it implies that our results are no longer strictly comparable with those of others. Our revised calculation is intended to reflect the children's gas exchange rather than that of child plus apparatus, and are thus smaller than would normally be obtained by conventional sampling of mixed expired gas. We have already come some way towards achieving this, as the method used in the 1986 paper separated the child's airway deadspace from that in the connecting apparatus, and also compensated for the effects of compressed gas in the tubings. These features have of course been retained.

In our revised calculation we do not subtract the rebreathed CO_2 volume from V_TCO_2, but instead use it to estimate F_ICO_2, i.e. volume of rebreathed CO_2 divided by alveolar tidal volume ($V_T - V_Daw$), in equation 1. This allows a fairer estimate of alveolar gas exchange. With the editor's permission we present the revised estimates. The number of patients has been increased to 58 since the 1986 paper was published. The table therefore presents the old and new ways of calculating deadspace in these 58, and also in the original 42 patients (values in brackets).

The change in method of calculation also affects Bohr's deadspace (V_DBohr), values for which were described in a second paper (3). V_DBohr is the noninvasive measure of deadspace obtained when endtidal PCO_2 is substituted for arterial PCO_2 in equation (1). The new values for V_DBohr are smaller, but the relationship between V_DBohr and V_Dphys is unaffected by the new calculations. However, the relationship between the airway deadspace and V_DBohr, in ml, is now

$$V_Daw = 1.9 + 0.687 \times V_DBohr$$

The r value for the regression is unchanged at 0.95. As before, the fraction V_Daw/V_DBohr was greatest in healthy children (frequently >0.80), and was smaller in those with a sloping phase III of SBT-CO_2. A sloping phase III is seen in left-right intracardiac shunting and mixed left-right and right-left shunting. Thus V_Daw/V_DBohr may be reduced in children with patent ductus arteriosus, atrial or ventricular septal defects, and other more severe defects. Atelectasis has a similar effect, presumably associated with overdistension of ventilated, non-atelectatic lung (4).

Which values should be referred to in future? When comparing our results with those of previous authors who have collected mixed expired gas, the old method of calculation $V_D$phys may be preferred. However, there are, as far as we are aware, no other values for $V_D$alv/$V_T$alv available for comparison, and therefore we suggest that the revised values for this variable are more suitable as "reference values", representing as they do a fairer measure of alveolar gas exchange under ideal conditions. The theoretical minimum value for $V_D$alv/$V_T$alv in healthy children is about 0.03 (Fletcher, in press): the normal children in this investigation almost approach this value.

Use of single breath tests to analyze deadspace has clear advantages over the Douglas bag method. $V_D$phys can be broken down into its component parts, and phase III slope, indicative of pathological gas elimination, can be measured. As more workers switch to this methodology, it is important that we are agreed on what we are measuring!

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Is the Message Getting Through?

To the Editor:

The article in *Anesthesia and Analgesia* by Kumar et al raises several questions not directly addressed in the paper as published (1). The large number of anesthesia gas delivery systems (AGDS) discovered with inadequate safety devices (e.g., O_2 analyzer, airway disconnect) is astounding (1). In this day and age where the smallest mishap can lead to a malpractice claim of extraordinary proportions, one would think that every AGDS machine would be properly monitored.

One must stop and wonder: Why were so many inadequate AGDS found? It is particularly curious that the authors did not correlate the nature of the discrepancies and the maintenance provider (i.e., manufacturer vs. contractor). Although data are provided on the size of the hospitals surveyed, no analysis is provided that correlate hospital size and the discrepancies found. Is information available on the nature of each anesthesia practice where these variances were found? Are the practioners recent graduates of residency training programs? Are the practioners Board-certified in anesthesiology? Were economic considerations a factor in the insufficiencies noted by these authors?

The proper education of our residents, continuing education of practicing anesthesiologists, and/or cost-benefit determinants will drive the engine for upgrading AGDS in this country. Articles such as that by Kumar et al and the threat of inspections by regulatory agencies, as well as the loss of malpractice insurance coverage with persistent noncompliance, will eventually remedy this situation nationwide. Nonetheless, the data presented are a disturbing signpost that the message about AGDS mishaps and patient safety may not be getting out.

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In Response:

We agree fully with Dr. Lawson's comment and perhaps "the message is not getting across". Our survey was not designed to look into qualifications or training of the anesthesia provider nor to assess their anesthetic practice. It was our impression that the majority of professionals working with older AGDS (Anesthesia Gas Delivery System) wanted to update or replace their AGDS, but were unable to do so because of financial constraints.

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Diltiazem Effect on Regional Function: Perfusion Pressure Rather Than Direct Effect?

To the Editor:

The publication of Leone and colleagues (1) suggest that diltiazem is responsible for regional dysfunction in the myocardium supplied by a critically constricted coronary artery. There is reason to believe that the worsening of function in this segment was due to a decrease in coronary perfusion pressure which followed the administration of diltiazem. The flow characteristics in a vessel with a critical stenosis, i.e., a loss of autoregulation (2), appears to be responsible for the decrease in flow and the latter correlates with postsystolic shortening as indicated. This confirms what we have published previously (3). Although they could not demonstrate significant differences in blood pressure, I suspect their comment ". . . may reflect the small study size rather than a lack of effect" to be correct.

However, although the perfusion pressure may be the problem (and not necessarily some unknown interaction), this study is still relevant to our clinical practice inasmuch as it demonstrates that a drug which is often quite useful may be associated with detrimental effects.

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In Response:

Dr. Coetzee has correctly drawn attention to the marked depression of global hemodynamic function evident in our study. This may, indeed, have caused the significant depression of regional myocardial function in the flow-compromised LAD region. Dr. Coetzee's view is that global hemodynamic depression seen, which decreased coronary perfusion, caused the regional dysfunction. However, diltiazem in combination with volatile anesthetics, in the absence of coronary stenosis is relatively devoid of global hemodynamic depreseive properties until extremely high doses are attained (1,2). We propose that this marked depression of coronary perfusion pressure and global hemodynamics was the result of diltiazem's adverse effects on the compromised apical myocardium. Because of the limits of our experimental preparation, the mechanism of diltiazem's effects on regional function cannot be determined, and therefore a direct adverse effect of diltiazem on ischemic myocardium, although plausible, cannot be proven. Whatever the mechanism, we share Dr. Coetzee's view that, despite its limitations, this study is relevant to clinical situations.

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Another Problem With a Stylet in an Endotracheal Tube

To the Editor:

Stylets are placed in endotracheal tubes to mold endotracheal tubes to the desired shape. Some anesthetists use styletted endotracheal tubes for difficult intubation; others use them routinely. We recently encountered an unusual experience with a styletted endotracheal tube.

The patient, an adult, scheduled for elective cholecystectomy, had an uneventful induction of general anesthesia with an uncomplicated, easy tracheal intubation. It was then found, however, that the stylet could not be removed from the endotracheal tube. On examination it was discovered that the tubing of pilot balloon through which air goes into the cuff had become enmeshed in the proximal end of the stylet that had been bent to avoid injury to the intubator's face or eyes during intubation (Fig. 1). Initially, efforts were made to pull the tubing out of the stylet and to straighten the proximal end of the stylet. This, however, risked damage to the tubing or pilot balloon. The styletted endotracheal tube was therefore taken out and the patient reintubated using a new endotracheal tube.

Since then we have made sure that, if a stylet is being used in an endotracheal tube, the air injection tubing does not become entangled with the stylet.

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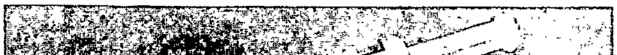

Figure 1. Styletted endotracheal tube showing air injection tubing locked into the proximal end of the stylet

Reverse Sellick Maneuver

To the Editor:

The administration of anesthesia for most elective intra-abdominal surgery, and almost all emergency intra-abdominal surgery, is associated with the insertion of a nasogastric tube. Most of the time, this insertion is simple, straightforward and uncomplicated. On a few occasions, the insertion of a nasogastric tube may be very difficult and associated with significant complications (e.g., severe epistaxis, etc). In patients in whom nasogastric tube insertion is not accomplished after several standard attempts, I have found that anterior displacement (lifting) of the cricoid cartilage or the "reverse Sellick maneuver" can facilitate the insertion of the naso-gastric tube. This technique has been used approximately 30 times over the past 12 months by several anesthesia personnel at our institution and appears to be successful approximately 75 to 80% of the times it is used.

The inferior constrictor muscle marks the anatomical beginning of the esophagus which is immediately posterior to the cricoid cartilage. Thus, anterior displacement of the cricoid cartilage may open the esophageal more widely and thus making passage of a nasogastric tube easier in patients in whom initial nasogastric tube placement is difficult.

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Cuffed Endotracheal Tubes in Pediatric Patients

To the Editor:

I have recently cared for several infants and children who have been intubated elsewhere with small (<5.0 mm internal diameter) cuffed endotracheal tubes and then transferred to the hospital where I work. These children developed severe subglottic edema and postextubation croup requiring reintubation with smaller uncuffed endotracheal tubes. Fortunately, all were subsequently extubated without incident.

I have consulted the well-known pediatric anesthesia textbooks in an attempt to determine age criteria for cuffed endotracheal tube usage.

As seen in Table 1, there are many different recommendations. There are also instances in which the text makes a specific recommendation but the accompanying table fails to denote at what age cuffed endotracheal tubes can be used. This is certainly a source of some confusion. None of the references in Table 1, however, recommend the use of cuffed endotracheal tubes in children under 5 years of age. Cuffed tubes in this age group are probably unnecessary and may be a potential source of tracheal injury. Why then, are small, i.e., <5.0 mm ID cuffed endotracheal tubes, still being manufactured?

Table 1.

Source	Recommendation
Gregory: Pediatric Anesthesia [1]	Table: Age 6–cuffed or uncuffed; Age 8–uncuffed; Age 10–cuffed.
Ryan: A Practice of Anesthesia for Infants and Children [2]	Text: Uncuffed Age <10 yrs. Table: No distinction between cuffed vs uncuffed.
Miller: Anesthesia[3]	Text: Cuffs unnecessary in children under 5 yrs. Table: No distinction between cuffed vs. uncuffed.
Berry: Anesthetic Management of Difficult and Routine Pediatric Patients [4]	Table: Cuffs in age 10 yrs or older.
Steward: Manual of Pediatric Anesthesia[5]	Text: No need for cuffed ETT <5.5 mm ID; no age mentioned. Table: No distinction between cuffed vs. uncuffed.
Levin: The Pediatric Anesthesia Handbook[6]	Text: Cuffed ETT with ages >6.7 yrs.

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Book Reviews

Anesthesiology, Problem-Oriented Patient Management

Fun-Sun Yao & Joseph F. Artusio, Jr. Philadelphia:
Lippincott, 1988, 702 pp, $45.00.

This book serves a unique and very valuable function: helping practitioners prepare for the oral examination of the American Board of Anesthesiology. Surprisingly this important feature is not stated in the Preface. Indeed, it seems to be studiously avoided even though the format is unequivocally patterned on the current Guided Case Discussion format of the oral Board examination. This book will appeal to candidates who are not familiar with oral exams in general or with the structure of this particular exam. It is especially valuable to candidates who did not think through clinical problems in this particular way during their residencies and now are faced with the problem of taking this exam, having been away from academia and in busy practice for some years.

This well-printed volume presents a wide-ranging set of 47 case discussions which follow a rigid format of a brief case description, pathophysiology and differential diagnosis, preoperative evaluation and preparation, and finally intraoperative and postoperative management. The degree of complexity and in-depth probing of the various chapters vary widely. In the chapter on asthma, there are 44 questions whereas there are only 11 each in the chapters on myasthenia gravis and prolonged apnea. Likewise some of the conclusions or answers must inevitably be controversial since the volume is heavily oriented clinically. The authors of the individual chapters are all members of the Cornell faculty and with varying degrees of experience and sophistication. Hence differences in quality are to be expected. Without intending to slight some authors, this reviewer liked the presentations of Yao and Tjeuw. Special mention must be accorded to the senior author, Joseph Artusio. Not only are his chapters well done, but this book is most likely his farewell contribution to our specialty, one in which he has served so well for 40 years (and at one institution at that!).

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Persistent Pain: Psychosocial Assessment and Intervention

N. Timothy Lynch and Sridhar V. Vasudevan, eds.
Boston: Kluwer Academic Publishers, 1988, 208 pp,
$35.00.

Pain is the single most common presenting complaint confronting the practicing primary care physician. Generally remitting spontaneously or yielding to available and appropriate therapies, when pain persists for no detectable organic cause or seems in excess of tissue damage, patients often suffer the fate of any frustrating object—resentment. While chronic pain patients can be empathically accepted if they have a clear organic etiology and/or struggle against disability (thus fulfilling the tacit "sick role" responsibilities inherent in the doctor-patient compact), patients who passively yield to invalidism or who cannot demonstrate a clear and proportionate physical etiology will often be labeled a "crock" or "gomer". Such patients not only frustrate physicians but are prone to doctor-shopping, self-medication/substance abuse and the iatrogenic side effects of heroic therapies such as, multiple surgeries unjustified by objective findings.

What can we do with the chronic pain patient? How can we manage such patients compassionately, avoid or minimize doctor-shopping, use the minimum of analgesic/psychotropic medication necessary and enhance the quality of life as well as the likelihood of return to work? Lynch and Vasudevan have gathered together practitioners of behavioral approaches to chronic pain to try to enumerate the principles, that govern their effects, including recognizing and accepting appropriate treatment goals, strategies for eliciting the patient's cooperation, recognition of good versus bad prognostic characteristics, recognition of the psychosocial stimuli that aggravate pain and/or increase/decrease compliance and recognition of foreseeable problems. Clearly the authors all owe an historical debt to one man and the text might have been subtitled: "A Festschrift in Honor of Wilbur Fordyce." It was Fordyce who first accepted the fact that diminishment of subjective pain as a clinical goal is not possible for many such patients and it should be conceived as separable from diminishment of cognitively/operantly-controlled "pain behavior." Patients who avoid coping with their pain in these maladaptive ways clearly show at least short-term decreased invalism and medication need and report improved quality of life.

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Persistent Pain raises some new considerations in the management of the chronic pain patient that bear some empirical scrutiny. A chapter by Schwartz makes the argument that subcortical damage in whiplash injuries, frequently undetectable by available imaging techniques but present on psychological testing, may account for some of Fordyce's "pain behavior" and/or make cooperation with psychologically rigorous treatment programs difficult. Getto's discussion of depression, and psychotropic medication use/misuse, in chronic nonmalignant pain patients begins the task of examining etiological factors. Clearly, diagnosis of depression or personality disorders in chronic pain patients is frequently complicated by the broad mix of psychotropics they use to deal with life. Detoxification is almost always required before evaluation can be completed. Having begun the task, Getto unfortunately avoids stepping beyond a presentation of the data regarding these critical questions. A bit of speculation on his part regarding the potential evolution and utility of diagnostic subgroupings would have been welcomed. Two chapters on counseling/psychotherapy with the chronic pain patient will be useful to the nonpsychiatric physician participating in the rehabilitation of these patients. Vasudevan and Lynch provide a series of pragmatic assumptions/strategies for managing the resistant patient and the chapters by Pilowsky and Ciccone & Grzesiak are primers on the psychotherapy of chronic pain. For physicians who find psychotherapeutic theory somewhat arcane, these chapters should demystify assumptions, goals and techniques. Grzesiak and Ciccone also review the use of relaxation, biofeedback and hypnosis in the treatment of both acute and chronic pain. In doing so they tackle, and largely disprove, the commonly held belief that emotionally-induced muscle tension/spasm can account directly for an increased intensity, duration or frequency of pain.

Critiques that might be leveled at this text are minor or characteristic of the field as a whole rather than specific to this text. One chapter on vocational assessment is abstruse and of limited value to the clinician seeking pragmatic guidance. There are a number of typographical errors in the text, an annoying but minor irritant. Most pressing for the field as a whole, it would seem, is the need for tightly reasoned and designed studies to sort out the etiological role of both physiological and psychological processes in benign, persistent pain. Where are the long term, prospective, "risk factor" studies of general populations and post diagnostic groups that might begin to help us better understand the causes and course of these patients? Of most concern is the absence of random assignment, nontreatment or standard treatment controlled studies examining the fate of patients not exposed to psychosocial interventions. These authors, alone, cannot be faulted for these failings. Despite the unanswered questions in this area, *Persistent Pain* is a good general introduction to psychosocial assessment and intervention in chronic pain. For the student, or physician unfamiliar with this arena, it will serve it's goal of providing a thorough overview.

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Cardiopulmonary Cerebral Resuscitation, Third Edition

Peter Safar and Nicholas G. Bircher. London: WB Saunders Co. Ltd, 1988, 464 pp, $18.50.

The third edition of this text is a revision and expansion of the preceding technique-oriented edition and provides comprehensive introduction to resuscitation. The first three of the book's seven chapters discuss basic, advanced and prolonged (postresuscitation) life support. Special resuscitation considerations, teaching resuscitation, organization of life support systems, and philosophical-ethical conclusions are the subjects of the succeeding chapters. The text includes 22 tables and 60 figures. The latter are illustrated and accompanied by substantive legends. More than 1000 references, including current literature, are cited. Techniques and management algorithms are presented in framed highlighted sections distinct from the text for improved readability. The book is well-indexed, permitting the reader to locate specific topics, some of which are referred to repeatedly.

The book was prepared for and sponsored by the World Federation of Societies of Anaesthesiologists, with input from the European Academy of Anaesthesiology. Principally, it appears to be the work of the two authors, Peter Safar and Nicholas Bircher, both of the International Resuscitation Research Center at the University of Pittsburgh. The book offers the reader an up-to-date summary of cardiorespiratory and cerebral life support from the perspectives of individuals with internationally acclaimed expertise on the basis of their research and clinical experience in the field. When the authors' recommendations differ from those of the American Heart Association (e.g., use of back blows in unconscious victims of airway obstruction, and 15:2 compression:ventilation ratio CPR by all rescuers, including two or more health professionals, for nonintubated patients) their rationale is discussed and referenced.

The scope of the text is not limited to cardiac arrest and resuscitation. It extends to life-threatening injuries and insults from many causes and cardiorespiratory and cerebral life support in many settings. Basic trauma life support is integrated with basic cardiac life support in the first chapter and advanced trauma life support is overviewed in the fourth chapter on special considerations. The text is as applicable to pediatric life support as it is to acute care of the unstable adult. Special sections are included on pediatric and neonatal resuscitation. Dr. Safar's conceptualization of basic and advanced life support and their distinction (based on therapeutic goals rather than whether adjunctive equipment is used) is logical and appropriate for the book's intended audience, physicians of all disciplines and nonphysician instructors of resuscitation. The text is not primarily written for neophytes in the field. This is illustrated by the sections on intubation and ventilation (discussion includes rapid-sequence intubation, awake-sedated laryngoscopy, fiber optic intubation, and high-frequency jet ventilation among other topics), artificial circulation (includes critical assessment of "new CPR" techniques and the C-A-B sequence), and drugs (two page discussion of the hypothetical role of calcium entry blockers in myocardial protection and preservation in cardiac arrest). The authors presuppose previous knowledge and experience in the reader as text descriptions are occasionally terse and may not include the precision or detail helpful to new learners.

The content is comprehensive and current; deficiencies are very few. This reader hoped for inclusion of anesthesia ventilating systems, e.g. Jackson-Rees and Mapleson D devices, in the section on ventilation and oxygenation; a more detailed description of the thoracic pump theory of blood flow during external chest compression; and more complete discussions on the issues of dextrose-containing IV fluids during resuscitation and bicarbonate recommendations vis-a-vis the low pulmonary blood flow produced during external CPR. Moot are the authors' recommendations for the use of cuffed tracheal tubes in children over the age of five years, lidocaine by infusion (vs intermittent boluses alone) in cardiac arrest, and external fist pacing in the conscious hypotensive patient with a bradydysrhythmia. This reader was puzzled by the placement of the discussions of open-chest CPR, emergent cardiopulmonary bypass, IABP, and ECM into the section entitled "Fibrillation Treatment" rather than in the section, "Circulation Support."

These few criticisms are mentioned constructively as they are far outweighed by the breadth and excellence of this one-of-a-kind text and do not detract from its overall value. The book's strengths are its comprehensive content, current and inclusive references to the scientific literature, and the chapters, "Prolonged Life Support" and "Special Considerations." It is highly recommendable to physicians of all specialties, who teach resuscitation or provide life support in the field, emergency room, operating suite, or intensive care unit. This comprehensive, up-to-date text should be on the book shelves of all medical and health-related libraries.

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Muscle Relaxants in Clinical Anesthesia

David R. Bevan, Joan C. Bevan and Francois Donati.
Chicago: Year Book Medical Publishers, 1988, 443 pp, $49.95.

This text is devoted exclusively to muscle relaxants and their place in anesthesia. Since this topic is well-covered in the standard anesthesia texts, the book aims for a treatment between the basic level and the reference collection of an active researcher. It begins with several background chapters including a history of the use of relaxants. As further background the authors develop the structure and function of the neuromuscular junction. They present the arguments for pre- and post-synaptic actions of the drugs, showing how these ideas developed. The authors make the point that a profusion of research has followed from standardized measurement techniques. This is followed by a brief section on clinical measurements where the differences between single twitch, tetanus and train of four are covered. The techniques of mechanical tension recording is compared with the more recently developed integrated electromyogram. Finally the authors compare the responses of muscle groups, an area in which they have made a significant contribution. Again they continue the theme of clinical relevance trying to put the great mass of research data into a coherent theme.

The basic principles of pharmacodynamics (dose—response) and pharmacokinetics (drug disposition) are reviewed without spending excessive time developing these complex subjects. Instead their clinical relevance is emphasized. For example, the effects of factors such as age and disease states on relaxant response and duration are emphasized.

The pharmacology of the available relaxants is a solid section on basic pharmacology which is at the heart of the book. Each drug is treated individually and the unique features that it presents are detailed. Differences between drugs are highlighted as well. The sections are well organized so that it is easy to search for information on a drug or topic of interest. The text is extensively referenced with many citations as recent as 1986.

The remainder of the book covers selected topics. A chapter is devoted to malignant hyperthermia including background, incidence, diagnosis, therapy and clinical management. Another chapter is devoted to antagonists of neuromuscular blockade. The book finishes with chapters on renal and hepatic disease, aging, drug interactions, and finally, neuromuscular diseases.

The book is reasonably complete in its treatment of the important topics related to the clinical use of muscle relaxants. The strong point of the book, however, is the pharmacology of these agents. This includes the effects common to all relaxants and the properties of individual drugs. This book will serve as a useful reference for the individual who needs more information than is found in the usual anesthesia text. It is especially valuable for its extensive bibliographies, which allow easy access to primary sources for those who need them.

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Practical Anesthetic Pharmacology, 2nd Edition

R. R. Attia, A. W. Grogono, F. R. Domer, eds. Norwalk, Connecticut: Appleton & Lange, 1987, 390 pp, $55.00.

Considering the many books addressing anesthesia-related subjects appearing annually, perhaps any book that makes it into a second edition can be considered a success. The second edition of *Practical Anesthetic Pharmacology* has much more that is positive. The second edition is a total rewrite rather than merely a revision. The number of pages have been increased by 33 percent and they are larger. The result: considerably more information.

The addition of a pharmacologist as a third editor has greatly increased the emphasis on pharmacology. In particular the introductory (and only new) chapter, "The Four Areas of Pharmacology," provides a concise summary of pharmacokinetics, pharmacodynamics, and dose-response and structure-activity relationships and provides a format that remaining chapters attempt to follow with varying degrees of success. In particular, the seven of 15 chapters written by the editors do follow this format effectively.

This book arrived when this reviewer was preparing his pharmacology lecture notes and he found that the chapters on analgesics, sedative hypnotics, and psychotropic agents provided a good overview of these topics. Each family of drugs was presented in sufficient detail, with a nice mix of classic and current references. However, for example, 18 pages does not afford adequate space to cover all aspects of the opioids. Nevertheless, the detail provided is excellent and in particular the "Practical Consideration" section, a highly desirable new feature of each chapter, is uniformly an effective way of highlighting the pertinent clinical points and certainly justifies the use of the adjective "practical" in the title.

The quotes that appear at the start of each chapter add a nice touch. Between the two editions the sources range from Aesop's Fables to Winston Churchill. "For some must watch while some must sleep," a quote from Shakespeare that appeared in the first edition, will be the theme of the Tenth World Congress of Anesthesia in 1992. However, this quote has been replaced by two other Shakespeare quotes in the second edition. In summary this remains a highly practical textbook on a subject which anesthesiologists, who practice a specialty which is truly "applied pharmacology," would do well to read.

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Management of Patients with Multisystem Organ Failure

Anesthesiology Clinics of North America, Volume 6, Number 1, March, 1988.

Vladimir Kvetan and Jeffrey Askanazi. Philadelphia: WB Saunders, 1988, 250 pp, $27.00.

This issue of ANESTHESIOLOGY CLINICS, edited by Drs. Vladimir Kvetan and Jeffrey Askanazi of the Department of Anesthesiology at the Montefiore Medical Center, New York, appears to be rather curiously misplaced. To an anesthesiologist, the title might suggest an issue addressing the concerns involved with providing anesthesia for patients with multisystem organ failure. Instead, this book sets out to describe the intensive care management of patients with the clinical syndrome of multisystem organ failure (MSOF). As such, this book will be of primary interest to those anesthesiologists actively engaged in the practice of critical care. Given this, one wonders why this issue was not placed in the series CRITICAL CARE CLINICS OF NORTH AMERICA, where it would also reach internists, surgeons and pathologists grappling with this multidisciplinary problem.

The editors' home institution is heavily represented in the list of contributors, with fourteen of the twenty-five authors drawn from there with the remaining contributors from the USA, Israel, and Finland. Regardless, there is a rather uneven style and emphasis across the thirteen chapters that comprise this book.

The organization of the chapters is also somewhat inconsistent. Dr. Christopher Bryan-Brown provides a succinct overview of MSOF, and raises some interesting questions-in the closing chapter. This would have been better placed at the beginning of the book, to provide some sort of central theme to tie together the many chapters that follow. The first chapter, Metabolic Effect of the Neuroendocrine Stress Response, is a densely written and encyclopedic review, which is then followed by a rather disappointing chapter on Hematologic and Immunologic Abnormalities Associated with Multisystem Failure. Here it seems that an opportunity has been lost to provide the reader with one or two chapters that would define and describe MSOF in a somewhat broad overview and attempt to tie together the metabolic and immunologic abnormalities in a way that would set the scene for the specific system discussions that follow. Next is an excellent chapter on Monitoring Metabolic Response in MSOF, which really described the difficulties in assessing energy expenditure and calorie requirement in critically ill patients. This should have more logically followed, rather than preceded one well written chapter on Nutrition in the Acutely Ill.

The book further suffers from the wide disparity between the styles and approaches of different authors. The chapter on Pulmonary Dysfunction in Multisystem Organ Failure (37 pages) is superb, with a detailed exposition on pathophysiologic alterations in pulmonary function including respiratory muscle failure in shock, abnormalities in respiratory drive, genesis of lung edema and hemodynamic changes. Treatment is well covered, with a good description of the interface between pulmonary and cariovascular systems. In contrast, the chapter on Acute Renal Failure (11 pages) is succinct to the point of being terse. Weissman and Hollinger provide an excellent review of anesthetic modification of the systemic responses to elective surgery, but they themselves admit that it is still unclear whether conclusions from this situation are applicable to patients with MSOF. Ultimately, the anesthetic management of patients with multisystem organ failure is reduced to one paragraph on page 229, which then contains an unfortunate typographic error: "metocurine or gallium (sic) should not be used in patients with renal failure . . ."

This reviewer is forced to conclude that this book is not about the anesthetic management of patients with multisystem organ failure. Nor, as a matter of fact, is it about the MSOF syndrome as proposed by the editors. There is not a single chapter that discusses the etiology and pathogenesis of MSOF itself. Perhaps the editors' greatest lapse is the lack of a chapter on multisystem interactions and their effect on sequential organ system failure, morbidity and mortality, or the effects of treatment of one system failure (e.g., renal) on another (e.g., pulmonary). Instead, this book largely describes the pathogenesis and treatment of (single) organ failure in the critically ill patient. There are some fine vignettes, some less so. In my opinion, this book would be helpful as a current reference for fellows undergoing critical care training, and as an update on several important topics for critical care specialists. However, it will be of little interest to most clinical anesthesiologists.

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Critical Care

J. M. Ciretta, R. W. Taylor, R. R. Kirby. Philadelphia: JB Lippincott, 1988, 1754 pp, $99.00.

Intensive care manuals, generally specialty oriented, have recently flooded the market. However, there are few comprehensive textbooks on Critical Care Medicine available. This 1754 page text with 166 contributors representing various specialties offers an unique multidisciplinary approach to critical care. Indeed, the editors represent the disciplines of surgery, medicine, and anesthesiology. The purpose of the text, according to the editors, is "to stimulate the reader's interest." With that as the goal, the book is a rousing success.

The book is divided into four parts. Part I reviews general principles entailed in the care of critically ill patients. The initial section opens with a discussion of the goals and objectives of intensive care. There are 10 chapters that established the framework for practice in an intensive care unit. This section identifies the roles of physicians and nurses on the ICU team and clarifies relations with other physicians, and family members. The next section presents a comprehensive review of resuscitation includingpathophysiology, management and outcome. In addition, many of the difficult medicolegal and ethical questions surrounding resuscitation are addressed. The third section contained in Part I of the text is especially useful to anesthesiologists. There are five chapters written by anesthesiologists that address perioperative concerns including pre-operative evaluation, effects of anesthesia in the critically ill and post-operative management.

The remainder of Part I reviews ICU procedures, monitoring modalities and diagnostic studies. This portion is particularly useful as a "how to" manual for the trainee assigned to the ICU. A unique feature of this text is a section in many of the chapters entitled "Immediate Concerns." This portion is an attempt to summarize the salient features of the chapter and to provide essential information about immediate problems, diagnostic measures, and treatment considerations. This is a challenging task and, unfortunately, is at best only inconsistently accomplished. Nonetheless, this section may, at times, serve as a ready reference guide for the trainee.

The second part of the text entitled "Systemic Problems" contains 33 chapters divided into five sections. The first section on metabolism and pharmacology provides a thorough review of pharmacologic principles with specific consideration given to metabolic response to injury and fluid and electrolyte management in the critically ill patient. The second section on nutrition is a comprehensive review of enteral and parenteral nutrition including assessment, nutritional requirements and monitoring of nutritional support. Unfortunately, discussion of nutritional support in the perioperative period was omitted. The third section consists of 13 chapters dealing with surgery and trauma involving various organ systems. This section provides an excellent review of perioperative concerns that the anesthesiologist can use as a ready reference source. Following a discussion of environmental hazards, the final section in Part II reviews infectious disease in the ICU. The nine chapters included in this section provide a current comprehensive review of infections in the critically ill.

Part III of the text provides a discussion of diagnosis, pathophysiology, procedures, and treatment of disorders ranging from myocardial infarction to rhabdomyolysis organized by organ system. The sections on the cardiovascular, respiratory and neurologic systems are the most extensive, though each section provides a detailed yet clinically relevant discussion of specific organ system disease.

The final part of the text, "Selected Topics in Critical Care" examines societal concerns in the ICU, including medico-legal considerations, and cost effectiveness. There is a very thoughtful discussion of these most sensitive issues. Unfortunately, there is no discussion or review of quality assurance programs for the intensive care unit, an area of interest and concern to the critical care medicine practitioner.

With few exceptions this is a well written, comprehensive, text that would be a valuable addition to the library of any physician involved in the care of critically ill patients.

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Anaesthesia at the District Hospital

Michael B. Dobson. World Health Organization (in collaboration with the World Federation of Societies of Anaesthesiologists), 1988, 136 pp, $18.00.

"This handbook is one of three to be published by the World Health Organization for the guidance of doctors providing surgical and anesthetic services in small district hospitals with limited access to specialty services. The drugs, equipment and procedures described conform with WHO and UNICEF recommendations." Dr. Dobson, a consultant anaesthetist from the Nuffield Department of Anaesthesia in Oxford, England, has had extensive experience in providing safe "austere anesthesia" in remote parts of the world.

The introduction to this useful text indicates that it is a limited text with limited aims. The target readership includes physicians at small hospitals who have limited anesthesia equipment and experience, and who are in a position of having to provide an anesthetic. The advice offered has been deliberately restricted to procedures that may need to be carried out by a young doctor with limited experience in anesthesia, using the facilities that can be reasonably expected in such hospitals. The text also discusses the type of patient that should be referred for specialized care at a higher level.

The first 46 pages of the book address the issues of airway management and resuscitation skills, including fluid management. The chapters on fundamental airway techniques and skills, and care of unconscious and anesthetized patients are well written and would be of use to a non-anesthesiologist whose responsibilities include resuscitation. The section on airway care and intubation, particularly the "failed intubation drill" are particularly good, and the clear illustrations would be of use to any anesthesiologist who must teach airway management skills to nonanesthesia physicians, recovery room nurses, or paramedical personnel.

The next 40 pages include patient assessment and general anesthesia equipment and techniques. Heavy emphasis is laid on the importance of thorough familiarity with a small clinical repertoire of safe anesthetic techniques. Although continuous-flow anesthesia machines, particularly the Boyle machine, are described and illustrated in detail, draw-over anesthesia machines and techniques receive the bulk of the attention. This is appropriate for the target readership, as draw-over apparatus is both simpler and easier to use than continuous flow machines, and is often cheaper to procure and employ. As this type of apparatus is not dependent on compressed gases, it is the only practical technique for areas where the compressed gas supply is limited or unreliable. Dr. Dobson makes the point that welder's grade oxygen; available in many parts of the world where medical grade oxygen is scarce, is essentially identical to medical grade oxygen. Ketamine anesthesia and anesthesia for emergency surgery are also addressed in this section. Ether, halothane and trichloroethylene are emphasized over the newer volatile agents, as expense and scarcity make isoflurane an unlikely choice under the circumstances for which this manual was written. The same philosophy is evident for all other pharmacologic agents mentioned.

Regional anesthetics receive 16 pages of attention, with excellent line illustrations of field blocks for cesarian section, extremity blocks, and spinal anesthesia. Epidural anesthetics fall outside of the range of this text and are not mentioned. There is a good section on management of spinal anesthesia, as well as the management of post dural puncture headache. A short section on choosing and planning anesthetic technique and postoperative care are also included, as well as a discussion of pediatric and obstetric anesthesia and resuscitation of the newborn infant.

Important medical conditions and their anesthetic implications, including anemia, hemoglobinopathies, malnutrition and cardiorespiratory problems are mentioned. Again, the emphasis is on the types of practical evaluation and implications of these conditions in a remote hospital, without sophisticated diagnostic or management resources.

The final sections include line drawings and information regarding oxygen concentrators and simple suction apparatus; both useful equipment. Lists for machine check-out of both draw-over apparatus and Boyle's machines are included, as well as a sample anesthetic record.

The author has done a nice job of distilling airway management, resuscitation, and "austere anesthesia" techniques into a short handbook for the nonanesthesiologist who is forced to provide such services. While the emphasis in the United States is on ever-increasing technological sophistication, it should be remembered that many successful anesthetics are performed in the world each day without the use of a single piece of digital-readout equipment or a single microchip. The techniques, apparatus, and skills outlined in this handbook are aimed at the nonanesthesiologist who is in the unenviable position of having no choice but to provide anesthesia. Dr. Dobson attempts to guide that physician to the safest techniques and agents possible under those conditions. This book will be especially useful for its target readership and for the many anesthesiologists who are now involved in anesthesia in developing countries. The airway and resuscitation chapters and illustrations alone are worth the very reasonable price of this book. It is recommended reading for anyone with an interest in the topic of "austere anesthesia" or draw-over apparatus.

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Near Misses in Anesthesiology: Lessons Learned

J. M. Lewis and T. Fontrier, Stoneham, MA: Butterworths, 1988, 98 pp, $16.95.

Anesthesia safety is a hot topic today. We anesthesiologists have recently learned that major mishaps, although rare, severely damage patients and generate expensive malpractice claims. Consequently we have published monitoring "standards" and have rushed to employ new and exciting monitoring technologies. One would hope that the current heightened awareness of safety among anesthesia practitioners will prove to be more than a passing fad.

One curious outcome of recent mishap studies is their failure to identify a subset of "bad apples" among anesthesiologists to which we can lay most of the blame. Anesthetic mishaps seem to be randomly distributed among all practitioners. Until we have more precise epidemiologic tools with which to challenge that conclusion, the safest working hypothesis is that we are all at risk, every day, for being the cause of serious morbidity.

In "Near Misses in Anesthesia," John M. Lewis and Toinette Fontrier of Bowman Gray School of Medicine take that hypothesis seriously. They present a collection of cases involving misadventures which "occurred in a totally random pattern and would suggest that even the *best* of clinicians with the *best* of intentions will still occasionally make mistakes."

Each of the 45 cases consume two small pages and follow the same format: A case history up to the point of decision followed by Resolution, Discussion, and a short list of references. Each episode is well documented and accurately presented. The references collectively make a good bibliography of anesthesia patient safety. Most of the more infamous mishaps are represented, each with a catchy title. "The Case of the Trembling Teacher," for instance, is a classic episode of—ah, but don't let me spoil it!

How does one effectively communicate distressing, depressing information? How better than with mystery and humor, as this little paperback demonstrates. By using self-deprecating humor ("The patient's hemodynamic parameters remain stable, but yours do not," p. 39) and concrete situational details which seem irrelevant at first glance ("Today you have a mild case of the sniffles . . . ," p. 17), the authors have personalized each episode. This was Ian Fleming's trick in the James Bond adventures (Bond's fans will recall that his martinis were "shaken, not stirred"). The sense of reality thus created leads the reader to "experience" the mishap as his own. For the same reason, each episode is an engaging mystery and a lot of fun.

But there is serious purpose in the fun. Too often anesthesiologists shrug off reported mishaps with the sentiment, "it could never happen to me." This book subtly teaches that mishaps are not the problem of "the other guy." To the extent that anesthetist-readers break into a cold sweat as they vicariously experience these adventures, the cause of anesthesia safety is advanced.

This is not a textbook or a reference manual. It is a tutorial well suited to its paperback thriller format. Rather than being placed on a library shelf it should be passed from hand to hand until it falls apart. All anesthesia practitioners, including those in training, will do their patients a favor by enjoying "Near Misses." I am told that the husband-and-wife team of Lewis and Fontrier are planning a sequel. I can hardly wait!

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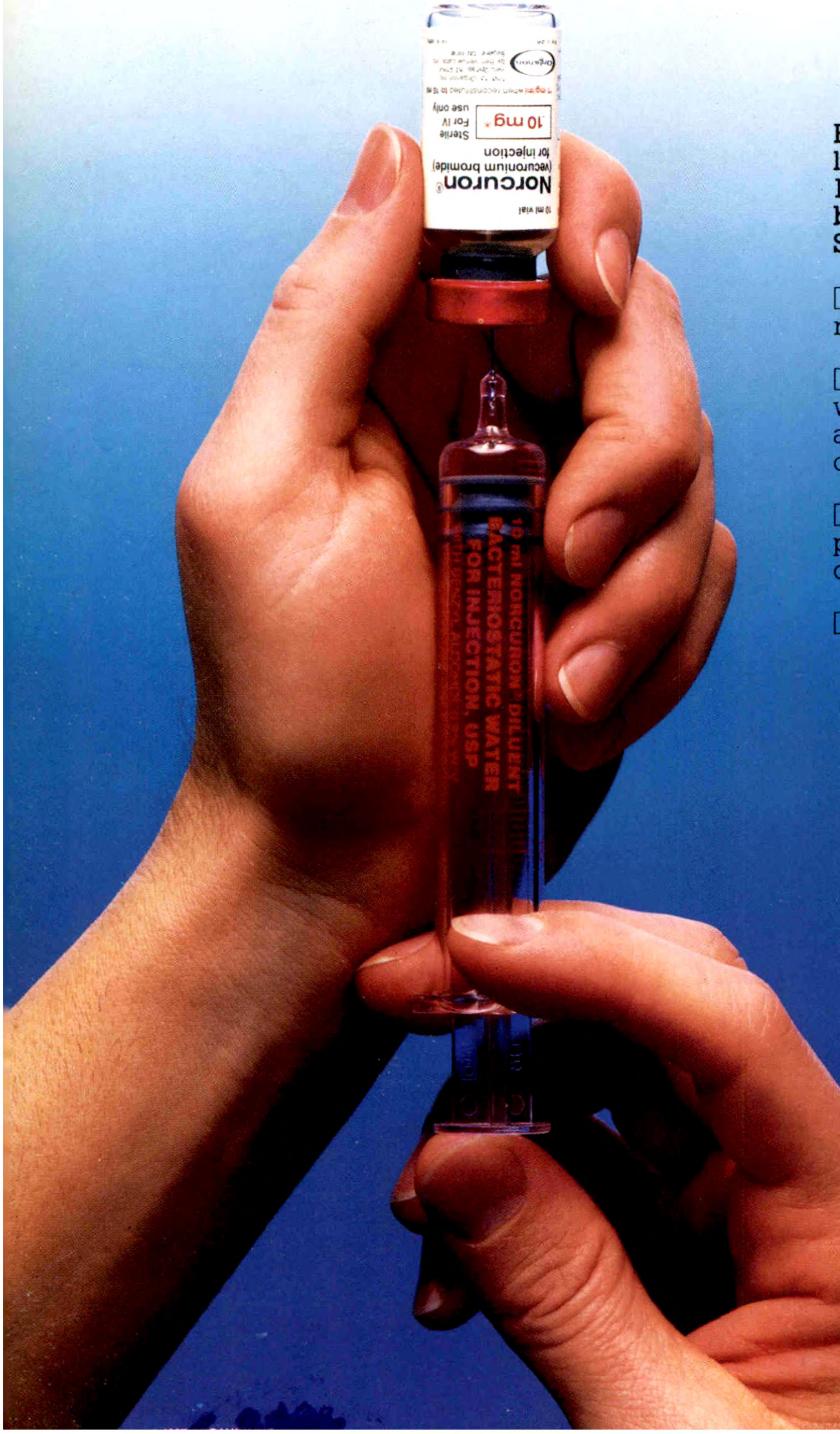

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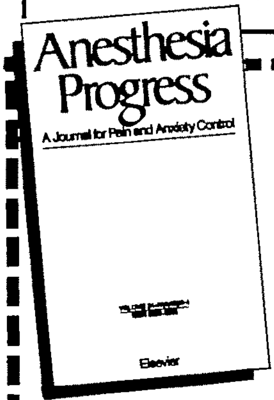

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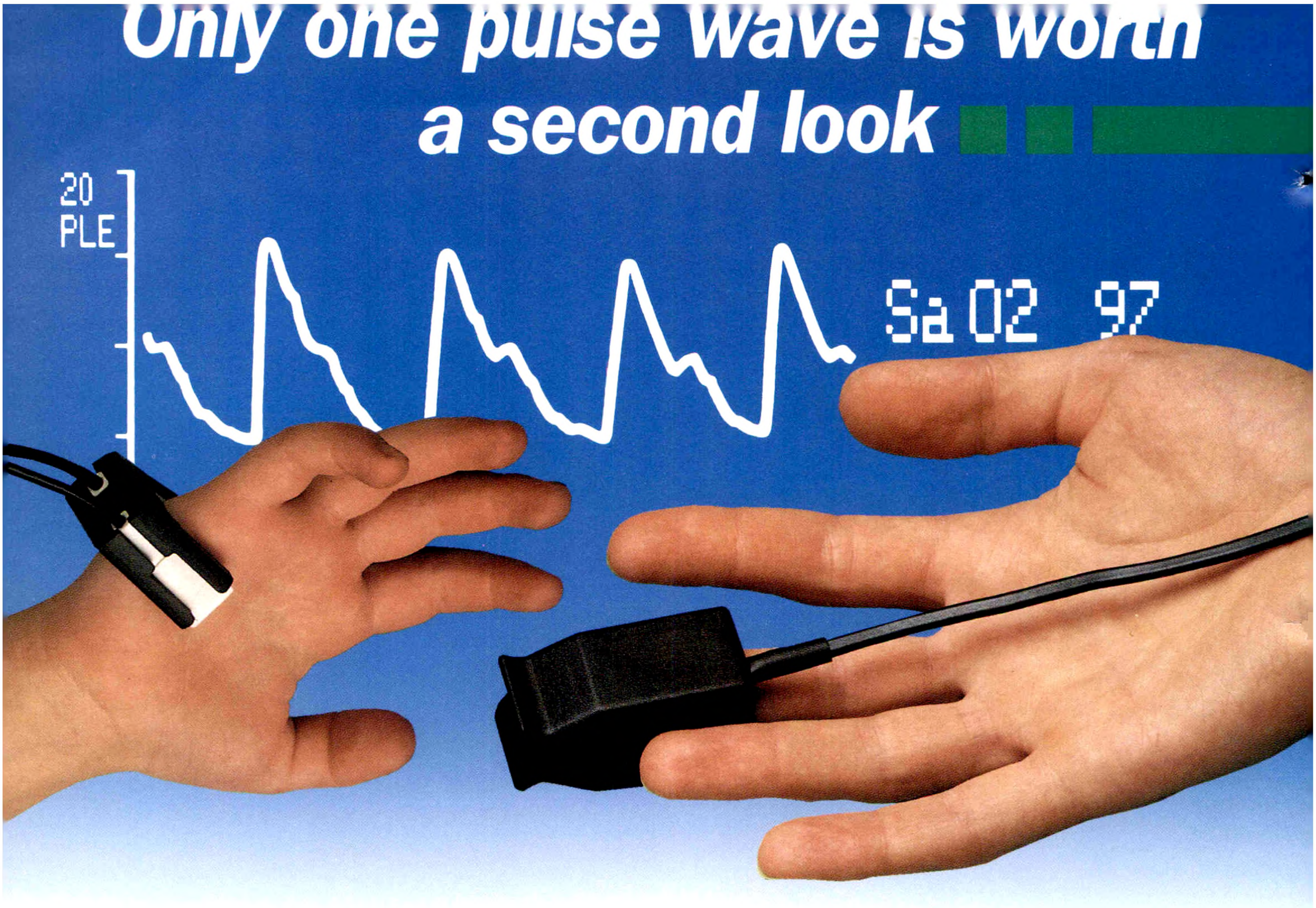

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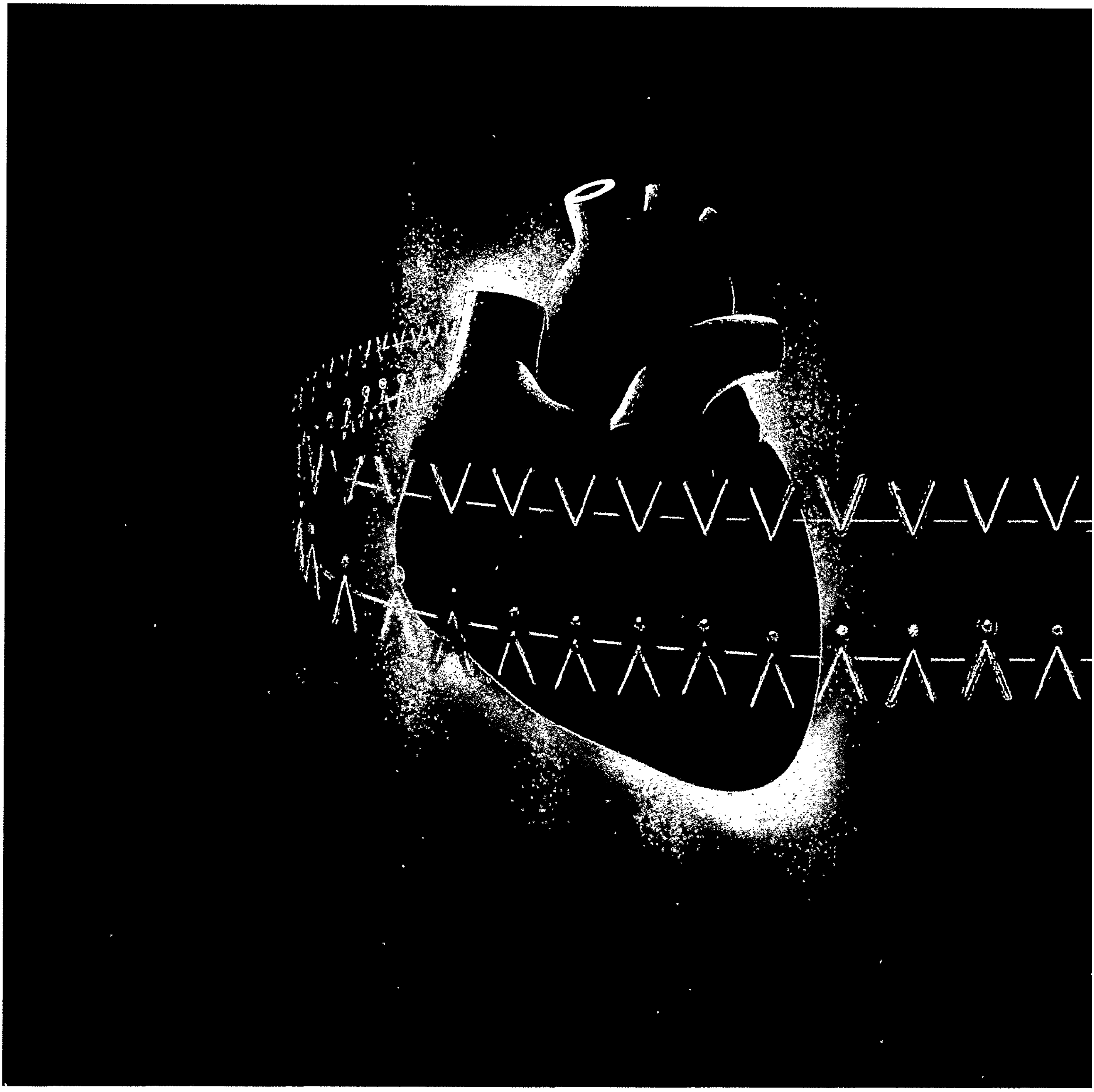

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Editorial

Nimodipine and The "No-Reflow Phenomenon"—Experimental Triumph, Clinical Failure?

Donald S. Prough, MD, and Curt D. Furberg, MD

Key Words: BRAIN, CEREBRAL BLOOD FLOW—cardiac arrest. HEART—cardiac arrest. PHARMACOLOGY—calcium channel blockers, nimodipine.

In this issue, Forsman and colleagues present the results of a clinical evaluation of the cerebrovascular effects of nimodipine following cardiac arrest (1). That study represents the next logical step in the assessment of the drug as a possible therapeutic agent to improve neurologic outcome following cardiac arrest in man. To date, nimodipine used experimentally in animals has been one of the most effective interventions for the reversal of post-ischemic hypoperfusion (PIH), one of the most commonly accepted mechanisms of neurologic injury following cardiac arrest. Forsman et al. build upon the demonstrations by Steen and colleagues that, in dogs (2,3) and primates (4), nimodipine will partially reverse PIH (2,3) and, if administered before or shortly following experimental global brain ischemia, will also improve neurologic outcome (2,4).

Because the study has generated negative clinical results, i.e., it did not improve neurologic outcome, it is tempting to dismiss it as a failure. That is certainly not true. It was not intended to be a large clinical trial, a research technique that attempts to answer definitively a small number of highly focused questions. Such a question for Forsman's study would be, "Does post-arrest administration of nimodipine improve neurologic outcome?" Conclusive answers to such questions usually require large numbers of patients, frequently acquired from multi-center trials. However, the clinical research that precedes definitive trials often generates other experimental and descriptive data which are heuristically invaluable for the generation of hypotheses for future research.

Forsman et al. provide such important data in at least three controversial areas. First, their study confirms the few available data that suggest that post-ischemic hypoperfusion (PIH) occurs in man in the first few hours following cardiac arrest and resuscitation. Second, it confirms that nimodipine antagonizes PIH in man as it had previously in experimental animals. Third, it suggests that antagonism of PIH in humans is not necessarily associated with dramatic improvement in clinical outcome.

Methodologically, these observations are dependent on the measurement of cerebral blood flow (CBF) using ^{133}Xe, a technique which has advanced substantially during the past decade. The original radionuclide clearance techniques for measuring CBF involved intracarotid injection of ^{133}Xe (6). Still useful in clinical situations in which intracarotid injection adds little additional risk (for instance, during carotid endarterectomy), that technique is necessarily impractical for general clinical investigation (7,8). Beckstead's original demonstration that PIH occurs in man utilized a modified Kety-Schmidt calculation performed on simultaneously collected arterial and jugular venous samples following a brief interval of ^{133}Xe inhalation (5). However, the development of mathematical techniques that correct extracranially counted gamma disintegration rates for arterial recirculation permits the administration of ^{133}Xe by inhalation (9) and by intravenous injection (10); Forsman et al. employed the latter in performing this clinical study. The intravenous technique, though yet to be widely employed in anesthesia and critical care re-

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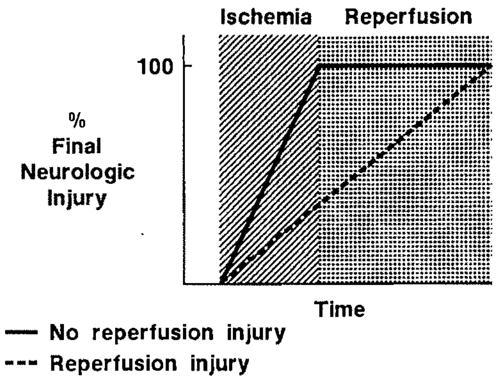

Figure 1.

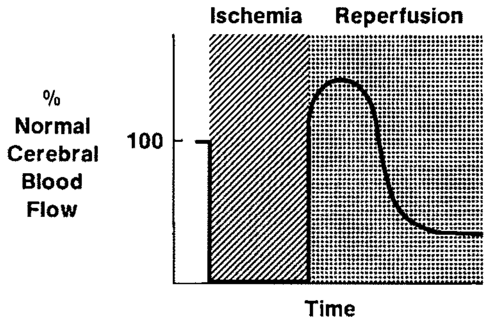

Figure 2.

search, provides a powerful tool for characterizing cerebral hemodynamics in patients at risk for neurologic injury (11).

The observations produced by this study (and probably of any post-arrest study intended to demonstrate neurologic benefit) also demanded precise study design. Based upon previous experience with animal experiments (2–4), the investigators concluded that, to be effective, nimodipine must be administered promptly after the initial insult. Consequently, patients were randomized to receive either nimodipine or placebo during transport to the hospital following resuscitation. This approach necessitated waiver of informed consent and restriction of the dose of nimodipine to reduce the risk of hypotension. One consequence of this study is therefore the demonstration that nimodipine in this dose range can be given safely in the early post-resuscitation interval without evidence of undesirable cardiovascular effects.

Thus, the authors employed a promising therapeutic agent in a sound protocol. How can one reconcile the evidence that nimodipine antagonized PIH with the failure to improve neurologic outcome? First, perhaps PIH is simply an epiphenomenon that does not itself contribute significantly to neurologic injury following global neural ischemia. Second, perhaps patients who have suffered cardiac arrest are sufficiently heterogeneous before arrest and so variably impaired following arrest that no trial of practical magnitude will satisfactorily demonstrate clinical efficacy in this setting.

Reperfusion injury is a fundamental theory underlying the intensive research into post-arrest neurologic care. Reperfusion injury is the concept that ischemic injury is not complete at the time that ischemia is terminated and perfusion is restored, but that damage progresses in the minutes to hours following resuscitation (Fig. 1). The concept is therapeutically optimistic; it suggests that prompt post-arrest therapy may limit or reverse the ultimate extent of neurologic disability. One of the earliest mechanisms proposed to explain reperfusion injury was that of PIH, or the "no-reflow phenomenon (Fig. 2)." Initially demonstrated in rabbits by Ames et al. (12), PIH was subsequently demonstrated in other species (4,13) and, in a limited series, in man (5). Consequently, numerous investigators have painstakingly investigated agents that might antagonize the intense, resistant cerebral vasoconstriction in the hope that improvement of post-ischemic CBF will limit neurologic injury. These are reflected in several representative recent publications (14–19).

As the study by Forsman et al. clearly indicates, reversal of PIH does not imply neurologic improvement. Beckstead et al. had previously suggested that PIH in man was insufficiently severe to explain permanent neurologic injury (5). In fact, in Forsman's series, the most profound increases in CBF occurred in patients who received nimodipine but never awakened. CBF did not immediately increase in those who received nimodipine and later awakened, although by six hours following resuscitation the flow was considerably higher than in those who had received placebo. Perhaps the most unexpected observation in this study is that patients who received nimodipine and ultimately awakened did so in about one-half of the time required by those who received placebo. Nimodipine enhanced the rate at which recovery occurred, without increasing the likelihood of recovery. Consequently, the results have generated the new hypothesis that, in less severely injured patients, PIH reduces CBF enough to produce *reversible* coma, and that nimodipine, by more rapidly improving CBF, results in more rapid awakening. However, these clinical data provide little encouragement for the concept that reversal of PIH will influence the mechanisms that produce irreversible cell death (Fig. 3), a circumstance in which increasing CBF has no effect on neurologic function.

The presumed mechanism of action for reversal by nimodipine of PIH is antagonism of ischemia-

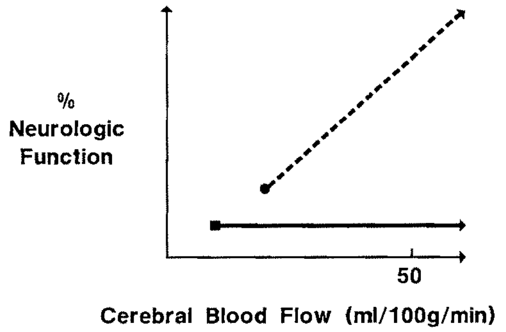

Figure 3.

induced increases in intracellular calcium. In addition to its probable effects on post-arrest cerebrovascular tone, calcium may play a central role in several other potential mechanisms of post-ischemic injury. Ischemia generates numerous biochemical reactions, through which it produces many putative mediators of post-ischemic reperfusion injury. Each potential mediator must be carefully evaluated to determine whether it actually contributes to progressive injury. That demonstration depends upon whether the putative mediator is capable of generating a potentially harmful physiologic response, whether it is generated in sufficient concentrations at the site of that response, and whether pharmacologic antagonism of the mediator attenuates the physiologic response. Most importantly, attenuation of the physiologic response must result in reduction of neurologic injury. Some mediators or related processes may produce reversible dysfunction (comparable to the concept of ischemic myocardial "stunning") (20), but may not produce mechanisms of reversible ischemic cell death.

This complicated problem is illustrated by one of the mechanisms mentioned by the authors as a possible explanation for the effectiveness of nimodipine. Calcium ions, accumulating intracellularly in excessive concentrations during and following neural ischemia, could stimulate phospholipase A_2, the enzyme that cleaves arachidonic acid, among other lipid membrane components, from cell membranes. Arachidonic acid is a substrate for the generation of multiple compounds in the prostaglandin and leukotriene series. One of those compounds, thromboxane A_2, is a potent cerebral vasoconstrictor and potentiates platelet aggregation. Intuitively, such a compound, if released in substantial quantities following global cerebral ischemia, could mediate PIH (21). As suggested by the authors, a calcium entry blocker that blocked the stimulation by calcium of phospholipase A_2 should reduce the production of the cerebral vasoconstrictor thromboxane A_2 and improve PIH. However, although nimodipine clearly antagonizes PIH in dogs (2,3), it exerts no demonstrable effect on the release from the canine brain of thromboxane A_2 following global cerebral ischemia (22). Therefore, the reversal of PIH by nimodipine appears to be independent of arachidonate metabolism.

As is frequently true in the rapidly expanding area of resuscitation research, one is left with more questions than answers. Is it possible that neurologic injury does not progress in humans following restoration of perfusion? Does PIH not contribute to reperfusion injury in man? Does it produce CBF-dependent reversible coma? Is the critical interval between recirculation and drug administration even briefer than the minimal time in this study? If moderate therapeutic efficacy is in fact present, how many patients must be studied to detect it?

The last question necessitates a brief overview of several fundamental principles of the design of clinical trials (for a more detailed description of those principles, see reference 23). In the first multicenter brain resuscitation clinical trial (BRCT I), the investigators assumed that 75% of the patients given placebos would survive to the analysis at 48 hours, and that 20% of the surviving randomized control patients would be conscious (24). Based upon the assumption that 40% of the surviving patients in the active treatment group would be conscious and the desire of the investigators to achieve at least 80% power and a two-sided significance level of 0.05, they calculated that 110 patients each would be necessary in the treatment and control groups (24). Therefore, one can conclude from these calculations that the sample size in the present study was obviously inadequate for an assessment of neurologic outcome. However, a more critical question is whether the assumption of a doubling of the recovery rate is realistic.

Heterogeneity of the population that has suffered cardiac arrest represents a most difficult problem for clinical investigation. Before cardiac arrest, the patients enrolled in the present study were certainly heterogeneous. More than half had important chronic disease before arrest. The arrest and resuscitation sequences added additional variability. The adequacy of cerebral oxygenation before resuscitation was probably highly variable, the quality of cerebral perfusion during cardiopulmonary resuscitation was certainly inconsistent (and probably at best produced barely acceptable CBF), and systemic perfusion following restoration of cardiac action frequently required pharmacologic support. Therefore, it appears that the assumptions used in the sample size calculation in BRCT 1 overestimated the maximal improvement possible with effective post-arrest therapy. In the present study, about one-third of patients had recovered to their pre-morbid level of function within four months following arrest (although nearly one-half regained consciousness at some time following resuscitation). Another one-third of the total number of patients (actually more than half of the number of patients who underwent lumbar puncture), those with levels of creatinine kinase BB exceeding 2.0 units/L in cerebrospinal fluid, never regained consciousness. One can assume therefore, that some proportion (perhaps one-third or greater) of patients will recover neurologic function if given careful standard therapy; some additional proportion (again, probably one-third or greater) will be irreversibly injured and their outcome determined regardless of subsequent treatment. The remaining proportion (probably at most one-third) perhaps could be improved partially by rapid institution of therapy that interrupts post-ischemic progression of injury. If 33% of the population potentially could benefit from treatment, and if the therapy actually improves the outcome in one-quarter of those patients (i.e., increases good long-term survivors from 33% to 41%), 1200 patients would be necessary for evaluation, assuming 80% power and a two-sided significance level of 0.05. As a consequence, the expense of a sufficiently large and well-designed study to demonstrate clinically significant post-arrest efficacy may preclude investigation even for highly promising treatments.

What then is the role for clinical post-arrest research? Should the demonstration of safety alone for a possible neuroresuscitative drug be sufficient to permit clinical use, if the probability of efficacy, based upon pre-clinical and clinical studies in more controlled circumstances, is sufficiently high? Perhaps, although the answers are unlikely to be that simple. Over the past decade, through the pioneering efforts of Dr. Peter Safar, a well-organized, multi-center group has been assembled that is uniquely qualified to conduct the necessary trials to investigate therapeutic efficacy (24). The remarkable efforts of that group, summarized as part of a recent symposium, provide a wealth of experience about clinical resuscitation research (25). Smaller clinical projects, such as the one in this issue of *Anesthesia and Analgesia*, will continue to provide new hypotheses which merit such comprehensive testing.

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Fifty-Seven Years Ago in
Anesthesia & Analgesia

M. B. Greene, J. Kaufman: Anesthetic and therapeutic nerve block by three-dimensions x-ray localization method. Current Researches in Anesthesia and Analgesia: 1932;11:241–51.

Rare indeed in medicine is the introduction of a technique or concept totally new, not based upon what has gone before. This article is, however, such a rare exception. It presents a new technique that continues, with further modification and refinement, to be used up to the present time. Certainly x-ray films were not new in 1932, but their use to guide the placement of needles during regional anesthesia was an innovation described in this paper, an innovation rapidly seized upon and subsequently further refined by others. This article did much to provide a method by which some of the more difficult, complex, and rather iffy therapeutic nerve blocks for the relief of pain could be converted to more predictable, reliable techniques that would assure that the nerves that one wished to block were indeed the nerves and the only nerves that were blocked by injection of local anesthetic or neurolytic solutions. The authors of this article used x-ray guidance in a different way, however, than most of their successors. After identifying the nerve to be blocked, the anesthetist marked the anatomic location in which the nerve was located with four strategically located small marks on the overlying skin. The patient was then moved to the radiology department, small lead markers were applied over the skin markings, and two x-rays taken from slightly different angles. The resulting films were then used by the anesthetist in a series of rather complex trigonometric exercises resulting in what amounted to triangulation for indentification of exactly where and how the needle should be inserted in relation to the skin markers in order to block the desired nerve. The system was so satisfactory that x-rays were not used, nor even needed, to determine where the tip of the anesthetist's needle lay after it had been inserted. The mathematics involved made it apparently almost inevitable that the needle had to be where it should be.

Effects of Nimodipine on Cerebral Blood Flow and Cerebrospinal Fluid Pressure After Cardiac Arrest: Correlation With Neurologic Outcome

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Andreas Skulberg, MD, PhD, Petter A. Steen, MD, PhD

FORSMAN M, AARSETH HP, NORDBY HK, SKULBERG A, STEEN PA. Effects of mimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: correlation with neurologic outcome. Anesth Analg 1989; 68:436–43.

Fifty-one patients were included in a blind randomized study to evaluate whether the Ca-blocker nimodipine could influence cerebral blood flow (CBF) or cerebrospinal fluid pressure (CSFP) during the cerebral hypoperfusion period that follows resuscitation from cardiac arrest and to determine whether changes in CBF correlate with neurologic outcome.

CBF measured 1 to 4 hours after arrest with the use of ^{133}Xe *intravenous was significantly greater with nimodipine than with placebo (27 ± 3 versus 13 ± 1* $ml \cdot 100\ g^{-1} \cdot min^{-1}$ *at 3 hours), but with no significant difference at 24 hours. There was no clinical evidence of seriously increased CSFP in any patient in either group the first 48 hours. Mean arterial pressure was significantly lower (86 ± 4 versus 101 ± 4 mm Hg at 3 hours), and antiarrhythmic drugs were used significantly less frequently in the nimodipine group than in the placebo group. Twelve patients in each group eventually regained consciousness. There was no significant difference in neurologic status between the two groups at any point, and no positive correlation between CBF in the hypoperfusion period and neurologic outcome.*

Key Words: BRAIN, CEREBRAL BLOOD FLOW—cardiac arrest. HEART—cardiac arrest. PHARMACOLOGY—CALCIUM CHANNEL BLOCKERS, nimodipine.

The prognosis for patients who are initially resuscitated after cardiac arrest remains poor. In most centers only about 15–30% survive with a moderate to good neurologic outcome (1,2), whereas an estimated 10–20% survive with permanent brain damage (3).

It has been speculated that much of the neurologic damage occurs not only during the initial ischemic event but also after re-establishment of the circulation (4,5). It is possible that the cerebral blood flow (CBF) remains inadequate despite restoration of a normal arterial blood pressure. After resuscitation from cardiac arrest, CBF has thus been found to be reduced to <50% of normal values in humans (6) and to 20% of control in dogs (7) for at least 6 hours. This decrease in CBF has been hypothesized as being linked to an increase in intracellular free Ca^{++} that might occur during ischemia (8). A high free calcium concentration might induce cerebral vasospasm (9), increased blood viscosity, (10) and platelet aggregation (11). Other possible deleterious effects of pathologically increased free Ca^{++} concentrations intracellularly include activation of nucleases causing DNA injury (12), production of the enzyme xanthin oxidase causing increased production of tissue damaging free oxygen radicals (12), and activation of phospholipases with breakdown of tissue phospholipids (5). The latter will cause increased tissue levels of arachidonic acid that can trigger a cascade of reactions resulting in release of prostaglandins and thromboxane, factors that might induce further vasoconstriction and platelet aggregation (8,12). Finally increased Ca^{++} concentrations might cause increased presynaptic release of excitatory amines, such as glutamate (13), resulting in further opening of postsynaptic

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Ca^{++} channels and even higher Ca^{++} concentrations intracellularly.

Because these events are likely to occur after reestablishment of the circulation (4), it might be possible to influence the cerebral pathophysiologic changes associated with cardiac arrest before the damage is fully developed. Interest has focused on Ca-blockers in the management of both cerebral (14,15) and cardiac (16) ischemia because they might inhibit an excess influx of Ca^{++} ions by blocking both receptor operated and potential sensitive Ca-channels in cell membranes (17).

Among the Ca-blockers, nimodipine has been found to increase CBF in dogs during the period of cerebral hypoperfusion (15). Neurologic outcome is also improved in dogs (15) when nimodipine treatment was initiated before and in primates (14) when the treatment was initiated after a period of complete cerebral ischemia.

This study was designed to determine 1) whether nimodipine influences CBF in patients when given after resuscitation from cardiac arrest; 2) whether there is any correlation between post-ischemic CBF and neurologic outcome; and 3) whether a clinically significant change in cerebrospinal fluid pressure (CSFP) occurs after cardiac arrest.

Methods and Materials

This was a prospective, randomized, controlled, and blinded study of 60 cardiac arrest patients resuscitated in Oslo either before reaching a hospital or in the Ullevaal University Hospital. Most of the outside-of-hospital arrests were resuscitated by personnel in ambulances that included an anesthesiologist; the others were resuscitated by paramedical personnel.

The study was approved by the ethical committees of Ullevaal University Hospital, the Norwegian Council for Science and the Humanities, and The Norwegian Medicine Control Authority. As the patients were comatose and in an emergency situation at the time of inclusion into the study, informed consent was not obtained, and the ethical committee of the hospital deemed it unethical to obtain consent retrospectively from survivors or the families of those dying.

Inclusion criteria included patients with cardiac arrest due to ventricular fibrillation or asystole, proven by electrocardiographic (ECG) monitoring and clinical appearance, who were resuscitated to the point where a mean arterial pressure (MABP) >70 mm Hg was maintained but who remained comatose without opening of eyelids in response to loud auditory stimuli or pain and without purposeful movements.

Criteria for exclusion included 1) Patients with head injury, brain surgery, or stroke in the 3 months before circulatory arrest. Excluded were also patients with suspected head trauma in association with the actual cardiac arrest. 2) Patients under general anesthesia or other CNS depressants at the time of arrest. 3) Patients with manifest cardiac failure within 5 hours of the arrest. 4) Patients less than 12 years of age.

Resuscitation was performed at the site of arrest following the guidelines of The American Heart Association (18).

The patients were tracheally intubated and manually ventilated until arrival at the hospital with an oxygen/air mixture (oxygen $>50\%$). External heart compression was performed until spontaneous circulation was deemed adequate. The ECG was monitored and patients with ventricular fibrillation were defibrillated with 250–360 J countershocks. Pharmacologic therapy was as clinically indicated, including, in most instances, epinephrine 1–4 mg intravenous or through the endotracheal tube and sodium bicarbonate 50–200 mEq intravenous plus, if indicated, atropine 1–2 mg intravenous and lidocaine 100–400 mg.

When circulation with a MABP >70 mm Hg was restored and maintained without mechanical or electric means for 5 minutes, eligible patients were entered into the study and a blinded randomized nimodipine/placebo infusion was started. In the few patients resuscitated by paramedical personnel, an intravenous infusion was started by a staff anesthesiologist after arrival at Ullevaal University Hospital.

The starting dose of nimodipine was 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($0.2\ mg \cdot ml^{-1}$), or the equivalent volume of placebo, delivered by an IVAC 700 battery infusion pump. The solvent for nimodipine was used as placebo (each 10 ml of solvent contained 1.5 g ethanol, 1.5 g polyethylene glycol 400, 0.02 g sodium citrate, 0.003 g citric acid, and 7 g water). The dosage was increased to 0.50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after 1 hour and continued for a total of 10 hours.

Two arrest times were recorded: minimal duration and total duration of arrest as estimated by the resuscitation team. CPR time was not included. Hypoxia time was defined as the period with severely reduced but not zero oxygen transport on the basis of clinical judgment and included the CPR time.

After resuscitation, intensive care included at least 12 hours of mechanical ventilation (Servo ventilator, Elema Schönander, Sweden). Normoventilation with $PaCO_2$ 38–41 mm Hg was attempted, with $F\ O_2$ adjusted to maintain PaO_2 >100 mm Hg with the least possible amount of positive end-expiratory pressure (PEEP) to minimize any possible effect of increased intrathoracic pressure on ICP. Blood gas tensions were measured with the use of an Instrument Laboratory 613 blood gas analyzer and were temperature corrected.

In the period after resuscitation, patients were immobilized by intravenous pancuronium when needed to control ventilation. Sedation with diazepam and morphine was used only when needed to prevent reaction on the tracheal tube and to help counteract hypertension and tachycardia when present. After 12 hours, attempts to terminate mechanical ventilation were initiated.

Cardiovascular monitoring included measurement of blood pressure with the use of an automated blood pressure monitor (Dinamap). With the goal of maintaining MABP above 70 mm Hg, Ringer's acetate solution or plasma was given as needed with dopamine added if hypotension continued. Arterial hypertension was not treated during the first hours when CBF was being measured, but thereafter was treated with a nitroglycerin infusion.

Ventricular arrhythmias were treated as needed with lidocaine 4 $mg \cdot kg^{-1} \cdot h^{-1}$ if no adverse reaction indicated change to another antiarrhythmic. Rectal temperature was continuously monitored. With the goal being maintenance of normothermia, paracetamol was given as needed for hyperthermia.

After intravenous injection of 10–15 mCi ^{133}Xenon dissolved in saline solution, CBF was measured by ten extracranial detectors and with an air detector sampling expired air for assessment of arterial and air passage ^{133}Xenon activity (19,20), with the use of a Novo Cerebrograph 10 a (Novo, Hadsund, Denmark). CBF in this study is reported as initial slope index (ISI) in $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (21). CBF was measured as soon as possible after admission of the patient to the cardiac care unit and repeated three times at intervals of 45–60 minutes. The longer interval was used in patients with extremely low flows. In these patients, the ^{133}Xenon dose was also increased in repeat measurements to achieve a sufficient peak count and to reduce the effect of the remaining activity because of the slow release of tracer. CBF was also measured 24 hours after the arrest when possible.

Intracranial pressure (ICP) was monitored when possible by an epidural transducer (Center for Industrial Research, Oslo, Norway). Spinal CSFP was measured with the use of a 22 G spinal needle attached to a fluid manometer 5, 24, and 48 hours after the arrest. Creatine kinase BB in cerebrospinal fluid was analyzed at the same intervals (22). Blood gas tensions were measured at the start of each CBF-measurement, 8, 24, 48 hours after arrest and when clinically indicated. Hemoglobin, hematocrit, blood glucose, and serum levels of Na^+, K^+, Ca^{++}, Cl^-, P^-, and Mg^{++} were measured on admission and then every 24 hours.

To evaluate the patient's physical and mental condition before arrest, existing hospital records were used and the family and/or the patient were/was interviewed. Physical condition was considered in terms of ability to walk outdoors without limitation. Cerebral function was considered good when a patient was able to perform activities of daily life normal for his/her social situation. If not able to do so, but still able to live at home, the patient was classified as having moderate disability. Severe cerebral disability was defined as present in patients hospitalized in a psychiatric or neurologic institution.

Neurologic evaluation was carried out after arrest and resuscitation according to the Glasgow-Pittsburg-Coma-scale (GPC-score), which in addition to the Glasgow coma scale includes evaluation of pupillary response, cranial nerve reflexes, seizures, and spontaneous breathing (23). Due to the use of controlled ventilation, breathing was not evaluated for the first 24 hours after arrest. Used this way, scoring had a minimum of 6 and maximum of 30 points on the GPC-scale. Forty-eight hours after arrest, breathing was included in determining the GPC score with a minimum of 7 and a maximum of 35 points. Conscious patients were tested for motor, sensory, and cerebellar functions with traditional clinical methods. All neurologic tests were performed by the first author.

Awakening time was defined as the first time when a patient correctly followed a simple command, such as "look at me and move your right hand."

All patients surviving the initial hospital stay were followed for a minimum of 4 months to evaluate whether they were back to their previous socioeconomic function or not, on the basis of interviews with patients, their families, and private doctors.

Statistics

For statistical comparison of physiologic variables between treated and untreated patients, a Student's *t* test for unpaired data was used. For statistical comparison of number of patients in defined groups, the chi-square test was used. Mann-Whitney Rank Sum test was used for comparison of CBF in patients that eventually did or did not regain consciousness and for awakening time.

Table 1. Status Before Arrest: Age,* Gender, Pre-existing Diseases, and Mental and Physical Abilities (number of patients)

	Nimodipine N = 25	Placebo N = 26
Age (yr)	65 ± 2	67 ± 3
Gender m/f	22/3	18/8
Pre-existing disease		
Hypertension	8	10
Angina pectoris	16	17
Myocardial infarction	12	11
Diabetes	3	4
Chronic bronchial asthma	5	1
CNS-pathology	7	5
Cerebral ability		
Good	15	21
Moderate	8	5
Disabled	2	0
Physical ability		
Walking without limitations	5	15†

*Mean ± SED; †P < 0.1.

Table 2. Circumstances of cardiac arrest and resuscitation.

	Nimodipine N = 25	Placebo N = 26
Location		
Out-of-hospital	20	25
First recorded ECG		
Ventricular fibrillation	17	22
Asystole	5	4
Not known	3	0
External countershocks		
0–3	17	15
>3	8	11
Patients with repeat arrests		
within 1 h	7	8
>2	3	4
Drugs used intravenous		
Epinephrine (mg)	2.4 ± 0.3	2.2 ± 0.3
Bicarbonate (mekv)	185 ± 19	172 ± 18
Lidocaine (mg)	153 ± 16	155 ± 16
Minimal arrest time (min)	4.0 ± 0.6	5.5 ± 0.7
Total arrest time (min)	6.0 ± 0.9	8.0 ± 1.0
Duration of hypoxia (min)	20.2 ± 4.8	18.5 ± 2.4

Mean ± SEM for doses and times.

Table 3. Spinal Fluid Pressures* 5, 24, and 48 Hours After Cardiac Arrest

	5 Hours		24 Hours		48 Hours	
	N	mm Hg	N	mm Hg	N	mm Hg
Nimodipine	21	11 ± 1	12	12 ± 1	13	13 ± 2
Placebo	22	13 ± 2	13	11 ± 1	13	13 ± 1

*Mean ± SEM.

Results

Of the 60 patients, 9 (5 nimodipine, 4 placebo) were excluded, 1 due to stroke, 1 due to CNS-depressant drugs taken before arrest, and 7 due to cardiac failure within 5 hours. Of the remaining 51 patients, 25 were given nimodipine and 26 were given placebo infusions.

There were no significant differences between the groups in age or sex (Table 1). Nor was there any difference before arrest in number of patients with systemic diseases or with CNS-problems, such as old head injury, stroke, seizures, Parkinsonism, or in cerebral ability categories. Physical function before arrest was significantly better in the placebo group.

The arrest-resuscitation situations were similar in both groups with no difference in location of patients, first ECG-pattern, number of external countershocks, recurrent arrests, doses of drugs, and arrest or hypoxia times (Table 2). The nimodipine infusion was started within 21 ± 4 minutes of restoration of spontaneous circulation, the placebo infusion within 16 ± 3 minutes.

In the nimodipine-treated group, four patients had cardiac arrest due to hypoxia, one due to hanging, one due to aspiration, and two due to acute bronchospasm. The remainder in both groups had primary cardiac arrests.

There were no significant differences between the groups in hemoglobin, hematocrit, blood glucose, or serum levels of Na^+, K^+, Ca^{++}, Cl^-, P^-, Mg^{++} (not tabulated).

CBF was significantly greater in the nimodipine group than in the placebo group when measured during the first 4 hours, but was not significantly different in the two groups when measured 24 hours after the arrest (Table 4). This was true both when based on mean CBF values for each patient and values from each of the ten regional ^{133}Xenon detectors. When the patients were divided into those that did and did not eventually regain consciousness, it was found that patients receiving nimodipine and never regaining consciousness had a significantly higher CBF than did those of the other three groups during the first two measurement periods (Fig. 1). Some measurements were discarded because of insufficient peak counts, remaining activity being >10% of measurement activity or because of technical failure.

MABP was significantly lower in the nimodipine group during the first 4 hours (Table 4), but the number of patients needing inotropic drugs were not significantly different in the two groups, 10 in the nimodipine and 8 in the placebo group. There were no significant differences in heart rate or temperature

Table 4. Cerebral Blood Flow (CBF) Expressed as Initial Slope Index, Mean Arterial Blood Pressure (MABP), Heart Rate (HR), and Temperature Measured Four Times During the First 4 Hours After Arrest and 24 Hours After Arrest

	N	Min After Arrest	CBF ml·100 g^{-1}·min^{-}	MABP mm Hg	HR min^{-1}	Temp°C
Nimodipine	25	117 ± 7	27 ± 3* (N = 22)	90 ± 4	94 ± 5	35.7 ± 0.2
Placebo	26	103 ± 6	20 ± 3 (N = 24)	99 ± 3	100 ± 5	35.9 ± 0.2
Nimodipine	25	164 ± 7	29 ± 3* (N = 22)	86 ± 3*	93 ± 5	35.7 ± 0.2
Placebo	26	148 ± 5	19 ± 2 (N = 24)	99 ± 4	95 ± 4	35.8 ± 0.2
Nimodipine	25	204 ± 6	27 ± 3* (N = 21)	86 ± 4*	89 ± 5	35.7 ± 0.1
Placebo	26	190 ± 6	13 ± 1 (N = 22)	101 ± 4	93 ± 3	35.8 ± 0.2
Nimodipine	25	242 ± 8	26 ± 2* (N = 17)	87 ± 4*	89 ± 7	35.7 ± 0.2
Placebo	26	231 ± 6	13 ± 1 (N = 21)	99 ± 4	89 ± 3	36.0 ± 0.2
		Hrs After Arrest				
Nimodipine	24	23 ± 2	45 ± 6 (N = 13)	91 ± 5	95 ± 4	38.1 ± 0.2
Placebo	26	25 ± 1	35 ± 3 (N = 5)	95 ± 4	89 ± 5	38.0 ± 0.1

*P < 0.05. Due to technical reasons, it was not possible to measure CBF in all patients at all specified times. The number of patients with CBF measurements are given in perentheses after the CBF value.

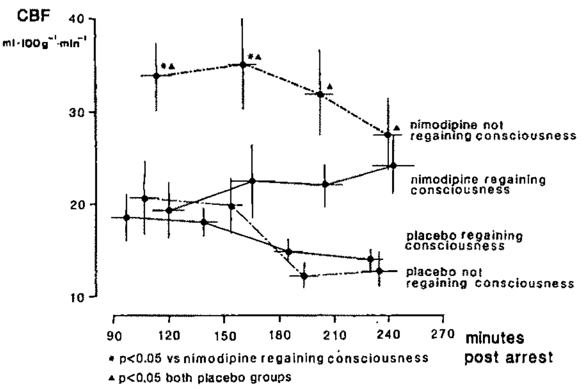

Figure 1. Cerebral blood flow (CBF) expressed as initial slope index (ml·100 g^{-1}·min^{-1}) during first 4 hours after cardiac arrest in nimodipine- and placebo-treated patients who did or did not eventually regain consciousness.

Table 5. Cerebrospinal Fluid Levels of Isoenzyme Creatine Kinase BB (U/liter) in 32 Patients 5-48 Hours After Cardiac Arrest

	CK-BB ≤2U/liter		CK-BB >2U/liter	
	Nimodipine	Placebo	Nimodipine	Placebo
Conscious	3	8	0	0
Not conscious	1	3	8	9

(Table 4). Blood gas tensions were not significantly different and were within normal range (not tabulated). The frequency with which intravenous lidocaine infusions were needed after initiation of the study was significantly less when nimodipine was given (N = 11) than that in placebo-treated patients (N = 21).

There were no significant differences in spinal CSFP between the two groups at any time and no single measurement of spinal CSFP above 20 mm Hg during the first 48 hours (Table 3).

ICP was measured in five nimodipine-treated and one placebo-treated patient. Four of the five nimodipine-treated patients had normal ICP throughout the study. One died and one regained consciousness after 24 hours; the two others, followed with ICP measurement for 72 hours, never regained consciousness. In one patient with anoxia due to hanging, ICP was normal for 12 hours and then slowly increased to 40 mm Hg before stabilization at 30 mm Hg. This patient had continuous seizures and CBF of 60 ml·100 g^{-1}·min^{-1} during the period with high ICP despite treatment with diazepam and barbiturates. In one placebo-treated patient, ICP was normal for 72 hours and then started to increase with transtentorial herniation occurring at 112 hours.

Creatine kinase BB levels in the spinal fluid, measured in 32 patients, were not significantly different in the two groups. No patient with CK-BB >2 U/liter regained consciousness (Table 5).

There was no significant difference in the amount of drugs or fluids given or urinary output in the two groups during the first 8 or 24 hours (not tabulated).

There was no significant difference in the Glasgow-Pittsburg-Coma Score between the two groups at any time (Table 6) or in neurologic outcome. Twelve patients in each group regained consciousness, one in the nimodipine group was not evaluated as he died a cardiac death 13 hours after arrest.

No patient with GPC score of ≤17 or with seizures 24 hours after arrest regained consciousness. Awakening time was significantly shorter in the nimodipine group than in the placebo group (Table 6). With

Table 6. Glasgow-Pittsburg-Coma Score (GPC) Less Than 2, 24, and 48 Hours After Cardiac Arrest

Hours after arrest	<2		24		48		—	
Min/max score possible	6/30		6/30		7/35		—	
	N	GPC	N	GPC	N	GPC	N	Awakening time*
Nimodipine	25	16 ± 0.4	24	20 ± 1	22	27 ± 2	12	18 ± 3
Placebo	26	16 ± 0.3	26	20 ± 1	25	27 ± 2	12	36 ± 8†

* Awakening time in hours after cardiac arrest; † $P < 0.05$.

Table 7. Neurologic Outcome 4 Months After Cardiac Arrest (number of patients)

	Back to Previous Life	Conscious in Institution	Not Conscious in Institution	Dead*	Not Evaluated
Nimodipine N = 25	8	0	1	15	1
Placebo N = 26	9	1	0	16	0

* 4 of the 15 dead in the nimodipine group and 2 of the 16 dead in the placebo group were initially cosncious but died of cardiac failure unrelated to cerebral hypoxia.

standard clinical neurologic examinations performed on all awake patients, only one (placebo) patient had a transient hemiparesis.

One patient in the placebo group was conscious 4 months after arrest but with severe brain damage. One patient in the nimodipine group died 6 months after arrest without ever having regained consciousness. All other patients surviving 4 months had recovered the same level of cerebral function as before arrest. None of the six patients dying from cardiac failure within 40 days had anoxic brain damage at autopsy.

Eleven patients in the nimodipine group and 14 in the placebogroup died from cerebral damage within 4 months, a clinical diagnosis that was confirmed in all cases in which autopsy was performed (9 versus 7) (Table 7).

Discussion

The present study confirms the observation by Beckstead et al. (6) that post-ischemic hypoperfusion occurs in patients resuscitated after cardiac arrest. Mean CBF was 23 ± 2 ml·100 g^{-1}·min^{-1} at 2–6 hours after arrest in the study by Beckstead et al. (6). It is impossible to compare this value directly with the present results as the measurement technique used by Beckstead et al. (6) was slightly different (height-over-area calculation after inhalation of ^{133}Xenon), and the number and exact timing of the measurements after arrest were not specified in their study. The mean CBF of 13 ± 1 ml·100 g^{-1}·min^{-1} in the placebo group 3–4 hours after arrest, despite an adequate blood pressure in the present study, corresponds well with the 70–80% reduction reported in dogs (7) assuming a normal CBF in humans of approximately 50 ml·100 g^{-1}·min^{-1}.

In our patients, nimodipine doubled mean CBF above levels seen with placebo administration during the hypoperfusion period, a finding similar to that previously reported in dogs (15). It should be noted that in our study, CBF was uniformly higher with nimodipine in all of the 10 areas studied with regional ^{133}Xenon detectors. Smith et al. (24) previously reported that although nimodipine increased mean CBF after severe incomplete ischemia in rats, the flow enhancement was regionally heterogeneous. This apparent discrepancy between our findings and those of Smith et al. might be due to a difference in species and type of ischemia, but also to the fact that our detectors gave CBF values for much larger regions than the small millimeter regional heterogenicity seen by Smith et al. in the rats. They also found uniformly higher CBF values with nimodipine for larger brain structures.

It has been assumed that an increase in CBF during the post-ischemic hypoperfusion period could improve the neurologic outcome (14,15). Therefore, when CBF is reduced below 8–10 ml·100 g^{-1}·min^{-1}, it appears that the brain is not able to maintain normal ionic gradients (25) with the attendant risk of causing permanent damage, and in the present study, some regional CBF values were indeed below 10 ml·100 g^{-1}·min^{-1} It is, therefore, of interest to note that there was not even a trend toward a correlation between CBF and neurologic outcome in the placebo group and that in the nimodipine group, CBF was in fact significantly higher in the patients that did not regain consciousness than in those who did. The interpretation of this finding must be speculative. It could indicate that the level of CBF usually seen during this period is not of primary pathophysiologic importance, and that the high CBF with nimodipine in the patients who did not regain consciousness indicates that those brains were indeed worse off with a completely disturbed autoregulation. If the hypoperfusion was of primary pathophysiologic importance hindering metabolic recovery, it would be expected that an increase in CBF was followed by an increase in CMRO$_2$. This was not found when CBF was increased with nimodipine in dogs (15). The hypothesis that decreased CBF after complete ischemia could be partly responsible for the final damage was not supported by the present study as there was no correlation between CBF and neurologic outcome. There was, furthermore, no significant difference in outcome with and without nimodipine in the present study, but it should be emphasized that the study was designed to evaluate CBF and a possible correlation between CBF and neurologic outcome and not whether the use of nimodipine as such would affect neurologic outcome. The Brain Resuscitation Clinical Trial I Study Group (BRCT I) (2) estimated, for example, that a minimum of 220 patients would need to be studied to achieve a significance level of $P < 0.05$ if a treatment doubled to 40%, an otherwise 20% incidence of good neurologic outcome assuming a statistical power of 80%.

Previous studies (14) in primates have demonstrated improvement in neurologic outcome with nimodipine, and an open pilot study (26) in humans with a historic control group gave encouraging results. In both these studies, the doses of nimodipine, up to 10 $\mu g \cdot kg^{-1}$ as a bolus followed by 0.5–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, were higher than those in the present study. The monkeys studied were young and healthy and the hearts were not stopped, only the cerebral circulation, whereas we gave nimodipine to patients with severe cardiovascular problems. This was the reason we, in agreement with the ethical committee and the manufacturer, decided to use smaller doses because a large bolus dose of nimodipine is known to cause hypotension. As there was not even a trend toward a better outcome with the present dose regimen for nimodipine, higher doses should probably be used in further studies of neurologic outcome.

The present results indicate that nimodipine is well tolerated in patients after cardiac arrest. MABP was significantly lower with the nimodipine infusion than with the placebo infusion, but remained above what is considered the lower limit of normal autoregulation, and, it is worth noting, these patients had significantly less need for antiarrhythmic drugs than the patients in the placebo group. The latter difference could be due to a possible protective effect of calcium entry blockers in myocardial ischemia. It seems likely that many of the same mechanisms involving a disturbed calcium homeostasis that might cause tissue damage are operating in cerebral and myocardial ischemia (8). Increased CSFP or ICP did not appear to be of primary importance in the patients in the present study. In the first 48 hours after arrest, there was in 104 measurements of CSFP in 45 patients and continuous ICP measurement in 6 patients only one instance of an ICP above 20 mm Hg (this in a patient with continuous seizures). This is in agreement with what has previously been found in dogs (7) and in another study (27) of 6 patients in which ICP increased above 20 mm Hg only in one patient, again in connection with seizure activity. Therefore, it does not seem likely that an increase in ICP will occur, causing further neurologic damage in the period after cardiac arrest in patients who otherwise would be likely to survive with an undamaged brain. It is very possible that some patients with irreversible damage finally die with an increased ICP, but it seems likely that it would be an event secondary to severe irreversible brain damage and not a primary event. One patient in our study developed transtentorial herniation 4.5 days after arrest without ever regaining consciousness.

That no patient with a spinal fluid level of creatine kinase (CK-BB) >2 U/liter regained consciousness is in agreement with previous observations (28).

In conclusion, hypoperfusion after cerebral ischemia, but no serious increase in CSFP, was seen in patients resuscitated after cardiac arrest. Nimodipine doubled mean CBF during this period of hypoperfusion. Nimodipine was well tolerated hemodynamically and appeared to reduce the need for cardiac arrhythmic drugs. There was, however, no correlation between CBF in the hypoperfusion period and neurologic outcome.

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The Response of Anesthesia Trainees to Simulated Critical Incidents

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GABA DM, DEANDA A. The response of anesthesia trainees to simulated critical incidents. Anesth Analg 1989;68:444–51

Using a comprehensive anesthesia simulation environment (CASE 1.2) we studied the response of anesthesia trainees (10 first-year residents and 9 second-year residents) to five simulated critical incidents: 1) endobronchial intubation; 2) kinked IV; 3) atrial fibrillation with hypotension; 4) breathing circuit disconnection; 5) cardiac arrest. Simulations were videotaped, and the response times for detecting and initiating correction of the problems were measured. Different problems had significantly different response characteristics. Breathing circuit disconnection and cardiac arrest were quickly detected (21 ± 17 seconds; 7 ± 5 seconds), and correction was begun quickly, although major errors in managing the cardiac arrest occurred in 58% of cases. Endobronchial intubation and atrial fibrillation took longer than the other problems to detect (105 ± 142 seconds; 111 ± 158 seconds) and to correct (555 ± 358 seconds; 365 ± 121 seconds). Intravenous kink was detected more slowly (238 ± 269 seconds) but once discovered was quickly corrected. The response of different individuals was highly variable; experience level was a significant factor for correction ($P = 0.03$) but not for detection of problems overall. Because of high individual variation, experience was not a significant factor in correcting any single problem. The data suggest that some types of problems are harder to handle than others and that individuals vary widely in their problem-handling abilities. Experience is a beneficial factor in anesthesia problem solving but not in a simple fashion. Vigilant detection of problems is only the first step in a complex response pathway that might be strengthened by improved protocols and repeated practice.

Key Words: EDUCATION. COMPLICATIONS; INTRAOPERATIVE—diagnosis.

Preventable human error is thought to be responsible for at least 50% of the 2000–4000 serious anesthesia-related mishaps that occur annually in the United States (1–3). These mishaps result in major morbidity (brain damage) or mortality and are often associated with substantial monetary awards to the injured parties (4). They therefore represent a significant problem for the profession of anesthesiology.

There are few studies of human error during the events surrounding anesthesia accidents. Cooper et al. have determined (5) that events that "required intervention . . . and did or could cause mortality or at least moderate morbidity" occurred in 14% of cases, excluding complex cases that went directly from the operating room to the intensive care unit. Responding to an intraoperative problem is therefore a common occurrence. Analysis of critical incidents, commonly called "near misses," has demonstrated 3,6–8) that many anesthesia accidents are avoided only by detection and correction of a potentially serious situation. In one study (3), approximately 7% of documented critical incidents resulted in a "substantive negative outcome," while the other 93% did not. The authors stated: "It is our impression from the process of collecting incidents, that most seemingly minor errors are not taken seriously and that risk management depends *almost solely on the anesthetist's ability to react instinctively and flawlessly every time a problem arises*" [emphasis added].

But how instinctive and flawless are these reactions? At what point in the cascade of events do problems get solved? Is it the same for every problem and for every individual? Are there different ways that individuals can fail to promptly detect or correct problems?

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Little is known about the process of responding to anesthesia problems. We intuitively believe that some are more difficult to handle than others and that individuals differ in their ability to respond to them, but there are few data on which to base these beliefs. Obtaining such data from the real world is difficult because critical incidents are neither common nor predictable, and objective data about events are rarely available. Testimony about the sequence of events and about whatever data were observed may be distorted so that "we soon start reporting not what happened, but *what must have happened*" (9). This lack of precise data and the fact that each incident is perceived as a unique occurrence make it difficult to establish normal responses to different problems based on *actual* cases of anesthesia mishaps.

We therefore developed a realistic anesthesia simulation environment whose technical characteristics have been described in a previous publication (10). Here we describe the application of the simulator system to present virtually identical anesthesia incident scenarios to multiple subjects. These serious incidents occur infrequently and cannot be ethically generated in real patients. In the simulator they can be created at will, and prospective unbiased data can be collected about the responses to them.

Using this technique we can provide data to support or undermine the intuitive beliefs we have about the abilities of anesthetists to react to problem situations. We can identify types of problems that are difficult to solve and the different ways in which individuals can fail to handle them optimally. We can observe choices of technique and of monitoring equipment and the effects of human–machine interactions. Any failures to appropriately observe or interpret clinical and monitor data can be observed.

We investigated the response to simulated critical incidents of a set of anesthesia trainees, some with little experience and some with much more experience, to answer the following questions:

When given the *same case description and intraoperative problem scenarios*:

Do all subjects choose the same monitoring and anesthesia techniques?

Is there a difference *between problems* for the rapidity of appropriate response?

Is *detection of the problem* the limiting step in problem resolution, or is diagnosis and therapeutic choice (*correction*) the limiting factor?

Are there differences *between individual trainees* or between *experience levels* in the rapidity of detection and correction of intraoperative problems?

What sources of information lead to detecting and beginning correction of complex problems?

Methods

All 30 first-year (R1) and second-year (R2) anesthesia residents from the Anesthesia Department, Stanford University School of Medicine (academic year 1987–1988) were invited to participate in this study. Nineteen volunteers (10 R1, mean experience = 6.6 ± 4.9 weeks; 9 R2, mean experience = 74 ± 12 weeks) gave written informed consent (as approved by the Human Subjects Committee) and participated over a 6-month period. Our simulator system, the Comprehensive Anesthesia Simulation Environment (CASE 1.2) has been previously described in detail (10). In brief, this system presented a virtually complete re-creation of a case requiring general anesthesia. Simulations were conducted in an actual operating room (OR) and used real OR equipment (except for the invasive blood pressure monitor, which used a functional replica on a Macintosh computer). The patient was represented by a thorax/intubation mannequin that allowed performance of many common clinical activities (laryngoscopy, tracheal tube manipulation, chest auscultation, etc.). The system included an operational intravenous line and required actual injection of appropriate drugs or saline from properly labeled syringes. In a previous report CASE 1.2 was evaluated as a highly realistic simulation of most aspects of anesthesia (10).

A test scenario (Table 1) was constructed that presented a clinically plausible case with several minor and major incidents. Each subject was presented with the same test scenario, although changes were made in real time to respond to unexpected actions or failures of the subject (e.g., failure to intubate the mannequin) or technical malfunctions of simulator components.

Each subject was presented with a brief patient description (Table 1) containing the patient's history, relevant physical examination, and laboratory findings. Subjects were allowed to choose anesthetic techniques (general anesthesia was required) and monitoring modalities. One request to monitor central venous pressure was denied because of a failure in the simulator CVP channel. All other requests for invasive cardiac monitoring (including pulmonary artery pressures) were granted.

After a briefing, a "warm-up" period was begun to acclimatize the subject to the simulation procedure. The subject wore a small lapel microphone, and a video camera recorded the anesthesiologist's activi-

Table 1. Test Scenario. The patient is a 65-yr-old, 70-kg man with a history of mild to moderate chronic obstructive pulmonary disease, angina upon moderate exertion, and hypertension. Medications include nadolol and hydrochlorothiazide. Physical examination is normal except for decreased breath sounds (no wheezing). Baseline vital signs: heart rate = 75, blood pressure = 145/95. Scheduled procedure is mastoidectomy. The surgeon requests the operating table be turned 180°

Time (hr:min:sec)*	Event
0:00:00–0:15:00	Anesthesia machine and equipment checkout; preparation of drugs and supplies
0:15:00–0:30:00	Anesthesia induction, turn table—requires long breathing circuit hoses (*Planned problem 1*)
0:30:00–0:40:00	Surgery begins, surgeon moves head repeatedly
0:40:00–0:55:00	Simulated endobronchial intubation (*Planned problem 2*) (Left mainstem bronchus occluded, CO_2 diverted to ventilated lung, SaO_2 decreases depending on F_{IO_2}—up to 1%/30 sec)
1:00:00	IV occluded (*Planned problem 3*)
1:02:00–1:15:00	Surgeon uses drill on mastoid ridge. Sinus tachycardia (100–120 beats/min), premature atrial contractions, atrial fibrillation (rapid ventricular response 120–140 beats/min), hypotension (mean arterial pressure to 50–55 mm Hg) (*Planned problem 4*)
1:10:00	Breathing circuit disconnection (*Planned problem 5*)
1:15:00–End	PVCs, ventricular tachycardia degenerating rapidly to ventricular fibrillation (*Planned problem 6*)

*Nominal elapsed time indicates the approximate target time for each incident. The actual elapsed times varied in each experiment.

ties with an electronic stopwatch image superimposed. The subject was instructed to "think aloud," verbalizing everything he/she saw, did, or thought (11,12).

During the "case" the simulation director actively played the roles of the surgeon and the circulating nurse. The simulation director answered the subject's questions about the simulation procedure with the minimum information necessary to allow the subject to continue functioning so as not to provide additional clinical clues (e.g., "Can I listen to breath sounds?"—"Yes").

The formal study began when the subjects requested the patient be brought into the room. Routine monitors (oximeter probe, ECG, BP cuff) were already in place, as was an intravenous catheter; these manual tasks were not simulated. Simulator responses to the subject's actions were based on a script that outlined the effects of various drugs or manipulations during each portion of the scenario. Where possible, responses were based on published data (13,14).

Where clinical data from the mannequin could be equivocal (e.g., during endobronchial intubation, auscultation of the left chest yielded markedly reduced breath sounds, but not silence) we waited for the subjects to repeat the observation at least once before disclosing the "true" physical finding (e.g., asymmetric breath sounds). This enabled us to observe problem-solving strategies without biasing the subjects prematurely.

Having recognized a problem, the subject could compensate for its effects and attempt to correct it. Criteria for "compensation" and "correction" for the planned problems are shown in Table 2. The script dictated that correct management of atrial fibrillation could mitigate the problem (decrease the ventricular rate) but not solve it (no conversion to sinus rhythm). Because we wanted to observe the response to a cardiac arrest, ventricular arrhythmias (culminating in ventricular tachycardia and fibrillation) occurred after atrial fibrillation and hypotension in *all* cases, regardless of the preceding management.

The videotapes were transcribed by the authors. Each act or utterance of the subject was listed with its elapsed time. From these transcripts and the original videotapes, each subject's response times for detection and correction of each problem were recorded. Time to detection was measured from the time of occurrence of an incident until the first detection of any manifestation of the problem. Time to correction was measured from time of occurrence until the beginning of one of the resolution actions. If a subject never detected or corrected a problem, his time was assigned as the longest time of any subject who did detect or correct it. The time interval between detection and correction of four problems was computed for each subject (Table 3). This interval was too short to measure accurately for cardiac arrest.

Since Advanced Cardiac Life Support (ACLS) protocols are widely accepted, management of the cardiac arrest was scored *perfect* if anesthetic gases were immediately discontinued and if either the 1983 or 1986 ACLS protocols (15,16) were followed. *Minor deviations* included small changes from the protocols for countershock energies, drug dosages, or the order of drugs; *major deviations* were failure to terminate anesthetic gases immediately, failure to countershock, or failure to administer epinephrine.

Response time data are presented as mean ± SD. A three-way analysis of variance (ANOVA) of response times was performed for three factors: levels of experience, problem, and time criterion (detection vs correction). Factors significant by three-way ANOVA

Table 2. Criteria for Compensation or Resolution of Planned Problems

Problem	Compensation criteria	Correction criteria
1. Short hoses	Move anesthesia machine Abort turning table	Request long hoses or hose extensions.
2. Endobronchial intubation	Increase F_{IO_2}	Pull back endotracheal tube.
3. IV kink	Insert new IV	Trace IV tubing to kink.
4. Atrial fibrillation	Administer fluid	Any of: verapamil, β-blocker, digoxin, pressors, cardioversion.
5. Circuit disconnection	"Ambu bag," mouth-to-tube ventilation	Reconnect.
6. Cardiac arrest		CPR, defibrillation, epinephrine, lidocaine.

Table 3. Time (Seconds) To Detection and Correction of Intraoperative Problems

	R1			R2			ALL		
	Detect	Correct	Interval	Detect	Correct	Interval	Detect	Correct	Interval
Endobronchial Intubation	137 ± 180	622 ± 376	485 ± 341	72 ± 90	484 ± 347	412 ± 350	105 ± 142	553 ± 358	449 ± 337
IV Kink	281 ± 298	484 ± 345	203 ± 245	191 ± 241	244 ± 247	53 ± 32	238 ± 269	370 ± 319	132 ± 191
Atrial Fibrillation	176 ± 199	407 ± 89	231 ± 180	39 ± 26	318 ± 140	279 ± 143	111 ± 158	365 ± 121	254 ± 161
Circuit Disconnection	25 ± 23	72 ± 46	47 ± 43	17 ± 4	32 ± 8	15 ± 6	21 ± 17	53 ± 39	32 ± 35
Cardiac Arrest	10 ± 5	NA	NA	4 ± 2	NA	NA	7 ± 5	NA	NA

R1 = First year residents (N = 10); R2 = Second year residents (N = 9); ALL = All subjects. Time to *detection* is from start of problem to first observation of any manifestation of the problem. Time to *correction* is from start of problem to making diagnosis and beginning correction. *Interval* is the difference between detection and correction time. For subjects who did NOT detect or correct a problem, their time was assigned the value of the longest time for any subject.
NA = not applicable (correction of cardiac arrest began immediately after detection in all cases)

were examined by two-way and one-way ANOVA and multiple comparisons (Fisher's protected least significant difference test), systematically excluding factors. Statistical significance was considered at $P \leq 0.05$.

Results

General Case Management

While all subjects were presented with the same patient description, there were differences in the monitoring and anesthetic techniques selected. Fifteen subjects chose an arterial line, and three requested a pulmonary artery catheter. Anesthetic technique was dependent on level of experience ($P < 0.01$). Twelve subjects used an inhalational technique, while seven (mostly R2) chose a balanced nitrous/narcotic technique. Subjects were informed on the case description sheet that the surgeon requested the table turned 180° (i.e., head away from anesthesia machine). Ten subjects, (5 R1, 5 R2) recognized the need to extend breathing circuit hoses before turning the table, while the other 9 subjects recognized the problem only during or after attempting to turn. Although confusion occurred, prolonged periods (>60 seconds) without ventilation did not occur.

Differing Response to Different Problems

Table 3 and Figure 1 illustrate the significant differences between the different problems in response times ($P < 0.001$, three-way ANOVA).

Endobronchial intubation. The initial manifestations of this problem were readily detected (mean time = 105 seconds) using a wide variety of modalities (Table 4). However, the earliest manifestation of the problem, an increase in the peak inspiratory pressure (PIP), was never observed by 11 subjects. The definitive diagnosis usually required bilateral chest auscultation of asymmetric breath sounds (16 subjects). Factors accounting for failure or delay in correcting this problem were 1) uncertainty about breath sound symmetry, 2) assumption of artifact or instrument failure as a cause of falling oxygen saturation, and 3) a desire not to interrupt surgery to ausculate the chest or change tube position. During simulation one R2 subject verbally listed every cause of increased PIP

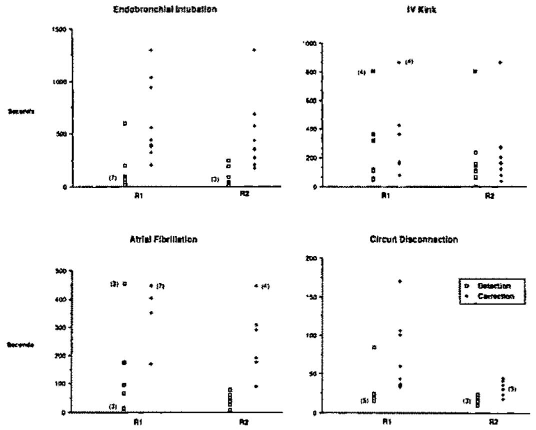

Figure 1. Response times from occurrence to detection (open boxes) and from occurrence to correction (crosses) for four intraoperative critical incidents. Each plot shows the distributions for 10 first-year residents (R1) and 9 second-year residents (R2). Where more than 2 subjects had nearly identical times, the number of subjects is shown in parentheses next to the data point. Note the different vertical time scales for each plot. There was a high variability in response times within each group; but, overall, experienced residents corrected problems significantly faster than did inexperienced residents.

Table 4. Modes of Detection and Diagnosis of Endobronchial Intubation

Observation Modality	First detection	Diagnosis
O_2 saturation	5	12
Esophageal breath sounds	5	11
Peak inspiratory pressure	4	11
End-tidal CO_2	2	13
Electronic spirometer	1	3
Mass spectrometer (N_2)	1	
Chest auscultation		16
Direct observation of tube		9
ECG heart rate		9
Blood pressure		9
Ask surgeon about tube status		4
Arterial blood gas		3

The modality of first detection was the manifestation of the incident first observed by the subject. Modalities of diagnosis are those observed after detection but before beginning definitive correction.

and decreased O_2 saturation except for endobronchial intubation.

Kinked IV. This problem was more difficult to detect (mean time = 238 seconds) but once detected was quickly corrected. However, six subjects entered the problem of atrial fibrillation without operational intravenous access.

Table 5. Modes of Detection and Diagnosis of Atrial Fibrillation

Observation modality	First detection	Diagnosis
ECG numeric heart rate	7	13
ECG waveform	5	16
Oximeter heart rate	3	5
Oximeter sound	3	6
Oximeter saturation		9
Arterial waveform		7
ST segments		3
Cuff blood pressure		2
Ask surgeon about blood loss		2

Table 6. Compliance with Advanced Cardiac Life Support (ACLS) Protocols

	R1	R2	All
Perfect	20%	11%	16%
Minor deviation	20%	33%	26%
Major deviation	60%	56%	58%

R1 = first-year resident ($n = 10$); R2 = second-year resident ($n = 9$); All = all subjects. Criteria for assessing compliance with ACLS protocols are given in the text.

Atrial fibrillation, hypotension. A supraventricular tachycardia was recognized rapidly by most (89%) subjects (mean time = 111 seconds). Even when the tachycardia was recognized, 53% of subjects did not diagnose atrial fibrillation or initiate appropriate treatment. The modalities of detection and diagnosis are shown in Table 5. Only one subject used the arterial tracing (which showed irregular beats) to support the diagnosis of atrial fibrillation. Factors that accounted for failure to diagnose or treat this problem were: 1) failure to examine ECG morphology and rhythm; 2) assumption that the irregularities in the ECG tracing were due to electrical interference; 3) assumption that hypotension was primarily due to hypovolemia (the "surgeon" admitted to a total blood loss of 200–300 ml) rather than atrial fibrillation itself.

Breathing circuit disconnection. Detection was accomplished quickly (21 ± 17 seconds), usually after one or more audible alarms had sounded (ventilator "low airway pressure"; spirometer "low minute volume"; real-time capnograph "no-breath"). Correction was also quick (53 ± 39 seconds).

Cardiac arrest. All subjects immediately (7.7 ± 5.2 seconds) recognized the lethal dysrhythmia and immediately began emergency treatment (cessation of surgery, cardiopulmonary resuscitation, etc.) There were, however, significant deviations from standard protocols (Table 6). Major deviations included failure to stop administration of anesthetic gases (8 subjects) and failure to administer epinephrine (6 subjects).

Detection versus Correction

The response time from incident occurrence to the initiation of correction was significantly longer than the time from occurrence to detection for endobronchial intubation, atrial fibrillation, and circuit disconnect (Table 3, Fig. 1). However, the time between detection and correction was very short for circuit disconnect (32 ± 35 seconds) as well as for IV kink and cardiac arrest.

Subject Performance

Subjects varied widely in their detection and correction of planned incidents. Figure 1 shows the distribution of detection and correction times, stratified by level of experience. Level of experience was a significant factor for the experiment as a whole ($P < 0.005$ by three-way ANOVA) and for time to *correction* of the problems ($P < 0.03$, two-way ANOVA). It was not a significant factor for rapidity of *detection* of problems, nor was it significant for the detection or correction of any individual problem state. R2 residents tended to be faster for each problem, but each group had its poor performers.

Discussion

These data are the first to describe how a population of anesthesiologists responds to the *same critical incidents*. The data might be valuable for several purposes, as noted in the following.

1. The results can help to determine which kinds of problems are easy or difficult to handle for inexperienced and experienced trainees, thereby suggesting where to concentrate our efforts at improvement. In this study each of the incidents had a different characteristic response time. Circuit disconnection and cardiac arrest were routinely detected and correction was started quickly, while endobronchial intubation and atrial fibrillation were more difficult to detect or correct.

We thus have evidence that technology can make an impact on such problems as breathing circuit disconnection, which 4 years ago figured prominently in Cooper's list (3) of critical incidents with substantive negative outcomes. The monitors and alarms now present on our equipment were highly effective in aiding even inexperienced personnel to prevent a negative outcome, especially since the corrective actions are well established and clearly take precedence over other considerations.

That endobronchial intubation and atrial fibrillation were more difficult to detect may reflect that there is no immediate warning of these conditions. Some signs of these problems (elevated PIP, ECG morphology, and rhythm change) were immediately observable but were initially missed by many subjects. Diagnosis and correction of these problems was slow in part because instrument readings (low O_2 saturation and irregular rhythm) were rejected as artifacts, and subjects failed to utilize multiple data sources (e.g., arterial blood gases to check low O_2 saturation; three to four sources of heart rate readings). Technology may therefore not always help, since several subjects, some with only a few weeks experience, incorrectly disregarded abnormal instrument readings as artifact or instrument failure [the "cry wolf" phenomenon (17)]. Confusion generated by multiple simultaneous audible alarms was also confirmed. These more subtle factors, rather than failure to *detect* a single lethal problem, may be the next frontier of anesthesia patient safety.

2. The results can help determine how "experience" is used in reacting to an intraoperative problem, leading to better educational protocols to train and maintain "safe" anesthesiologists. In this study, experience in anesthesia *was* a significant factor in the overall rapidity of appropriate correction of the test problems. The high variability among subjects masked this factor for individual problems. In determining how the response to problems may fail, *the imperfect behavior of the outliers may be more meaningful than the mean performance of the groups*. It is not surprising that experienced residents did better than inexperienced ones. The more interesting finding is that *many* inexperienced subjects did respond appropriately to the problems while *some* experienced subjects did not, despite a presumed substantial difference in clinical knowledge.

Data from other industries (nuclear power plants, space flight (18–20) suggest that dynamic problem solving often consists of the application of already compiled procedures for recognizing and correcting problems. Deep reasoning about cause–effect or structure–function relationships is generally used only when standard procedures are perceived by the operator to be either inapplicable or unsuccessful. We speculate that the response to acute intraoperative problems is largely accomplished using precompiled procedures and that even inexperienced trainees can incorporate some of these procedures and retrieve them under appropriate situations. However, even experienced residents did not *always* initiate appropriate correction of some problems such as endobronchial intubation and atrial fibrillation. Incidents like these may involve more complex procedures to arrive at one of many possible diagnoses or to choose appropriate actions in the face of a complicated set of constraints, while IV kink, circuit disconnection, and cardiac arrest lend themselves to simpler procedural solutions. *The responses of experienced attending staff and private practitioners to these types of incidents remain to be determined and should shed more light on this hypothesis.*

If precompiled procedures do make up a large portion of responses to intraoperative problems, then these procedures, including guidelines of priorities of action, should be more formally defined, compiled, and presented during anesthesia training and continuing education, rather than handed down in an ad hoc manner as random "clinical pearls."

3. The data suggest that even when widely acknowledged emergency procedures are formally taught, it will take repeated practice to maintain these skills. The R1 residents had all received ACLS training in the previous 4 months, the R2 residents all within the previous 18 months. Yet the implementation of the ACLS protocol was full of errors, both minor and major (Table 6). On review of the tapes, subjects who committed major deviations often recognized their failures (i.e., "Oh no, I forgot to turn off the anesthetic."). These errors demonstrate the fragility of our knowledge and skills when confronted with a high-stress situation we rarely encounter. Besides repeated practice, perhaps a system of real-time computer-based decision support would be helpful to remind the practitioner what to do during problem situations. Such a system's utility could be tested only by using a realistic simulation environment because of the rarity of the serious incidents that could benefit from its displays.

4. The data provide a new perspective on the belief that faulty vigilance is the primary cause of anesthetic mishaps (21–26). *Vigilance* is defined as *sustained attention* (2), and because of the nature of the experiment and the short duration of the scenario, a lack of sustained attention was not observed in this study. Subjects vigilantly detected early manifestations of most problems, but they did not always go on to rapidly recognize and correct them. Delays and errors still occurred in deciding if a problem was real and what to do about it. These data then support our prior contention (2,27) that vigilance is only the first of many steps in successful recovery from an evolving problem. Improvements in patient safety should focus on diagnostic and corrective protocols as well as on vigilant detection.

5. Our results might begin to provide a better framework for analyzing *actual mishaps*, yielding a more realistic basis for deciding what responses can reasonably be expected from the vigilant and careful anesthesiologist, and what truly represents seriously deficient performance. The standard of care is currently based on educated guesses of how one should have behaved in a given situation. Data from studies such as ours can help to ensure that these guesses have some basis in empirical fact.

How well do these results represent what occurs in real life? We do not know for sure, since there are few data on the success or rapidity of response to similar real problems. Although the simulator and the scenario were judged realistic by the subjects, they are far from perfect, primarily because of technical limitations in the current simulator (e.g., no spontaneous ventilation, breath sounds audible only at specific external sites, etc.) (10). As long as the subject knows it is a simulation, his or her performance might be affected. Data from the nuclear industry (28) have shown that power plant operator response times were up to six times longer in field tests than during studies in high-fidelity stimulators. The state of high vigilance in a simulator experiment may thus be likely to yield a "best-case" bound on anesthesiologist performance.

Is the simulator system of demonstrable educational benefit? Although education was not the purpose of our study, many of the residents who participated felt that it was a highly educational experience and indicated this in their written evaluations of the session (10). The investigators also received an education. We discovered which elements of anesthesia were assimilated correctly by new residents, and which appeared to be distorted. We saw the foibles of more experienced trainees; they surely mirror those of their mentors as well. Nonetheless, this was a study of the problem solving ability of trainees, not of a simulator-based educational program. The ultimate utility of realistic simulation as an educational tool remains to be investigated.

The anesthesia practitioner is the crucial element in safe patient care. The data indicate that we *cannot* assume that patient safety will be maintained solely by instinctive and flawless reactions of the vigilant observer. The realistic simulation environment provides an appropriate laboratory for the study of the anesthetist's human limitations to safety, but these investigations have just begun.

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In Vitro Metabolism of Mivacurium Chloride (BW B1090U) and Succinylcholine

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COOK DR, STILLER RL, WEAKLY JN, CHAKRAVORTI S, BRANDOM BW, WELCH RM. In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. Anesth Analg 1989;68:452–6.

The in vitro rates of metabolism of mivacurium chloride and succinylcholine in pooled human plasma were compared. In addition, the rate of metabolism of mivacurium in buffered solutions of butyrylcholinesterase (E.C. 3.1.1.8) and acetylcholinesterase (E.C. 3.1.1.7) was determined. Succinylcholine concentrations were measured spectrophotometrically, and mivacurium concentrations were determined with a high-pressure liquid chromatographic assay. The hydrolysis of mivacurium in plasma followed first-order kinetics, and the rate of hydrolysis decreased as plasma was serially diluted. The Michaelis–Menten constant (K_m) for mivacurium metabolism in plasma was 245 μmol/L, and the maximum velocity (V_{max}) was 50 U/L; the K_m for succinylcholine was 37 μmol/L, and V_{max} was 74 U/L. At comparable multiples of the K_m the hydrolysis rate of mivacurium was 70% of that of succinylcholine. Mivacurium was metabolized significantly in solutions containing butyrylcholinesterase, but only minimally in solutions containing acetylcholinesterase.

Key Words: NEUROMUSCULAR RELAXANTS—Succinylcholine, mivacurium. ENZYMES—butyrylcholinesterase (plasma cholinesterase).

Mivacurium chloride (BW B1090U), a new short-acting nondepolarizing muscle relaxant, and succinylcholine are metabolized in human plasma, presumably by butyrylcholinesterase (plasma cholinesterase). Hydrolysis of mivacurium is thought to produce a quaternary monoester and a quaternary amino alcohol; these breakdown products are pharmacologically inactive (1). The duration of neuromuscular blockade at equi-effective (i.e., equal multiples of the ED_{95}) doses is two to four times greater with mivacurium than with succinylcholine (1–3). This difference in duration of action may be related to differences in enzyme kinetics between the two relaxants. We were therefore interested in determining the substrate–velocity relationships of the two relaxants at various enzyme and substrate concentrations in human plasma. In addition, we investigated the metabolism of mivacurium in buffered solutions containing purified butyrylcholinesterase or acetylcholinesterase.

Materials

Choline chloride, horseradish peroxidase, 4-aminoantipyrine, choline oxidase, human butyrylcholinesterase (plasma cholinesterase, E.C. 3.1.1.8), and human acetylcholinesterase (true cholinesterase, E.C. 3.1.1.7) were obtained from the Sigma Chemical Company, St. Louis. Succinylcholine dichloride and mivacurium chloride (BW B1090U) were obtained from Burroughs Wellcome Co. Echothiophate iodide was obtained from Ayerst Laboratories, Inc. All other chemicals were reagent grade.

Five units of fresh human plasma were pooled, and serial dilutions (1/2, 1/4, 1/8, and 1/16 strength) of plasma in phosphate buffer (pH 7.4) were made. These stock plasma solutions were stored frozen in 2-ml aliquots. Aliquots of the pooled plasma and the various dilutions were assayed for butyrylcholinesterase activity and dibucaine inhibition by Smith, Kline, Beckman Laboratories using a standard spectrophotometric technique with acetylthiocholine iodide as a substrate. Human acetylcholinesterase (100

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U/ml) or butyrylcholinesterase (100 U/ml) was also prepared in phosphate buffer.

Experimental Procedures

In preliminary experiments, mivacurium (18 μmol/L final concentration) was incubated at 37°C in 50 ml of pooled undiluted plasma, 5 ml of phosphate buffer, or 5 ml of phosphate buffer with either acetylcholinesterase or butyrylcholinesterase. At timed intervals (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 10, 15, 20, 25, 30, 45, and 60 minutes) aliquots were withdrawn and added to tubes containing a cholinesterase inhibitor (25 μl of a 7% solution of phenylmethylsulfonylfluoride or 0.25% echothiophate) and then frozen to −70°C. Mivacurium concentrations were determined in each aliquot by a sensitive, specific high-pressure liquid chromatographic spectrofluorometric assay modified from an atracurium assay (4). Alcuronium was used as an internal standard.

We obtained estimates of the K_m for succinylcholine and mivacurium in human plasma by incubating various concentrations of succinylcholine (0.1–8 mM) with 50 μl of plasma in buffer or various concentrations of mivacurium (1–450 mM) in 250 μl of plasma for 20 minutes at 37°C. The reactions were stopped with echothiophate iodide. The hydrolysis of succinylcholine was measured by a modified spectrophotometric assay (5,6). We did not reconfirm that the hydrolysis rate of succinylcholine was linear over time. The hydrolysis reaction of succinylcholine by human plasma was coupled with choline oxidase and peroxidase in the presence of 4-aminoantipyrine and phenol to produce a red quinone dye (6). The absorption of the quinone dye produced was measured at 500 nM with a Gilford spectrophotometer (Model 240). Appropriate blanks were used to correct for the spontaneous hydrolysis of succinylcholine. Standard curves relating choline concentration and absorbance were constructed using choline chloride.

The enzyme activity for succinylcholine and mivacurium at each substrate concentration was expressed as micromoles hydrolyzed per minute per liter of plasma at 37°C [μmol·min^{-1}·L^{-1} or units per liter (U/L)]. Plots of substrate concentration and enzyme activity (U/L) for the two relaxants with crude enzyme were made. The apparent K_m for the enzyme preparation and each relaxant was calculated from the reciprocals of velocity (1/V) and substrate (1/S) using a Lineweaver–Burke plot. The maximum velocity (V_{max}) of each reaction was calculated. These parameters were not estimated graphically.

Several concentrations of succinylcholine and mivacurium at defined multiples of the K_m (0.1, 1, and 2 times the K_m) were incubated with either 50 or 250 μl of the undiluted plasma or the diluted plasmas. The samples were again incubated for 20 minutes at 37°C, and the reactions were stopped with echothiophate. The enzyme activities (μmol·min^{-1}·L^{-1}) were calculated.

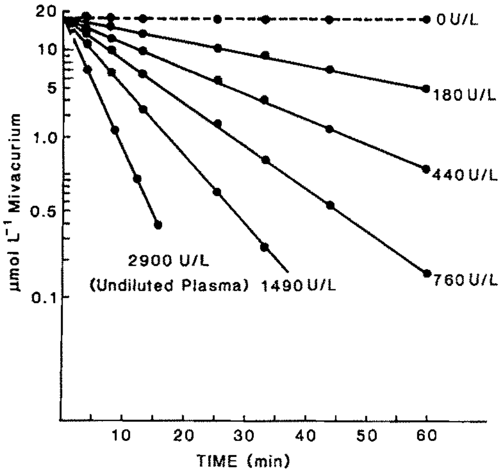

Figure 1. Solid lines: In vivo plasma decay curves of mivacurium over time in normal human plasma and in plasma samples diluted with phosphate buffer to reduce the plasma cholinesterase activity. Plasma cholinesterase activity of 1490 U/L is associated with 1/2 strength plasma, 760 U/L is associated with 1/4 strength plasma, 440 U/L is associated with 1/8 strength plasma, and 180 U/L is associated with 1/16 strength plasma. The starting concentration of mivacurium in the plasma samples (t = 0) was 18 μmol/L. Dots (solid circles) represent mean values. Standard deviations have been omitted for clarity but are discussed in the results. The determinations were made at pH 7.4 and 37°C. Dotted line: Data for buffer solution with no plasma added.

All experiments were replicated at least four times. The interassay precision for succinylcholine had an average standard deviation of 2 U/L, and that of mivacurium was 0.3 U/L; both had a coefficient of variation of about 5%.

Results

The pooled, undiluted human plasma had a butyrylcholinesterase activity of 2900 U/L, and the activities of the diluted plasma preparations were 1490, 760, 440, and 180 U/L, respectively. The hydrolysis of mivacurium (18 μmol/L) at physiological pH and temperature in plasma with the various butyrylcholinesterase activities followed first-order kinetics in that a plot of the logarithm of the mivacurium concentration over time was linear (solid lines in Fig. 1). There was no spontaneous hydrolysis of mivacurium in buffer alone over 1 hour (dotted line in Fig. 1). The hydrolysis rate of mivacurium with pure butyrylcholinesterase (100 U/ml) was 3.45 μmol·L^{-1}·min^{-1}, and

Table 1. Relation Between Mivacurium and Succinylcholine Concentrations and Crude Enzyme Activity

Plasma butyrylcholinesterase activity	Succinylcholine activity (U/L)			Mivacurium activity (U/L)		
	0.1 K_m	1 K_m	2 K_m	0.1 K_m	1 K_m	2 K_m
A (2910 U/L)	7	37	74	5	26	50
B (1490 U/L)	4	33	38	4	18	31
C (760 U/L)	—	18	24	3.0	16	24
D (440 U/L)	—	1	9	2	12.6	18
E (180 U/L)	—	—	5	0.6	12.6	13

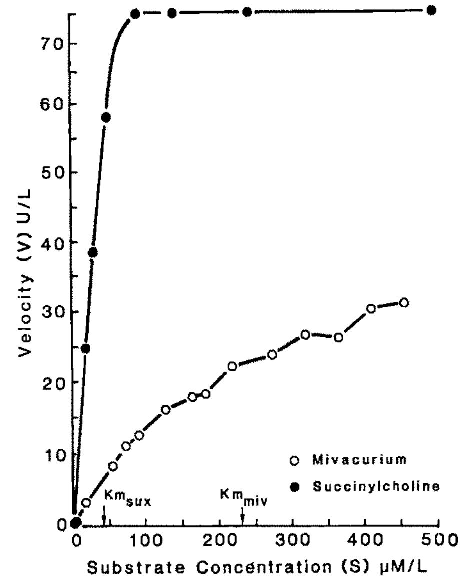

Figure 2. Relation between mivacurium (0) or succinylcholine (·) concentration on plasma and rate of in vitro metabolism in normal human plasma. Each data point represents the mean of at least 4 determinations. Standard deviations and data points omitted for clarity.

Table 2. Relation Between Butyrylcholinesterase Activity and Mivacurium Half-Life

Butyrylcholinesterase activity (U/L)	Mivacurium half-life (min)
2900	3.1
1490	5.6
760	9.4
440	17.0
180	34.4

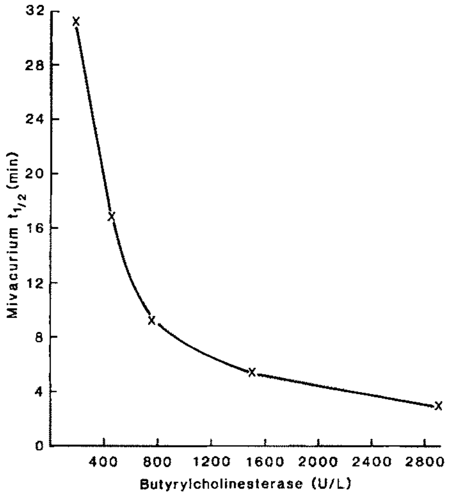

Figure 3. Mivacurium in vitro half-life at 0.1 Km concentration in normal plasma and plasma with reduced butyrylcholinesterase activity.

with pure acetylcholinesterase (100 U/ml) it was 0.15 μmol·L^{-1}·min^{-1}.

The K_m for mivacurium in plasma was 245 μmol/L, and the maximum velocity (V_{max}) was 50 U/L (Table 1 and Fig. 2). The K_m for succinylcholine in plasma was 37 μmol/L, and V_{max} was 74 U/L (Table 1 and Fig. 2). At mivacurium and succinylcholine concentrations equal to 0.1, 1, and 2 times the K_m concentration there was a decrease in velocity as crude enzyme activity increased (Table 1). We estimated the in vitro half-life of mivacurium at the 0.1 K_m concentration at the various butyrylcholinesterase activities from each decay curve in Figure 1. The half-life of mivacurium increased in a hyperbolic fashion as butyrylcholinesterase activity decreased (Table 2, Fig. 3). The in vitro half-life of mivacurium at the 0.1 K_m concentration (25 μmol/L) in pooled, undiluted human plasma was 3.1 minutes (Fig. 3). The hydrolysis rate of succinylcholine could not be determined at the 0.1 K_m concentration in plasma with markedly reduced enzyme activity because of the limited amount of color formed.

Discussion

This study documents that mivacurium is hydrolyzed in vitro by normal or diluted human plasma and by purified butyrylcholinesterase (plasma cholinesterase) but only minimally by acetylcholinesterase (true cholinesterase). The study also demonstrates that mivacurium is not degraded in buffer solution lacking enzyme. Butyrylcholinesterases of human plasma are nonspecific and are capable of hydrolyzing a variety of substrates at different rates. The Michaelis–Menten constants (K_m) for succinylcholine and mivacurium determined in human plasma differ significantly; the maximum velocities (V_{max}) differ as well. The velocity–substrate relationships for succinylcholine in undiluted plasma are comparable to those reported by others (5,6). The graph of velocity versus substrate concentration of succinylcholine shows rapid enzyme saturation with a well-demarcated plateau of velocity. On the other hand, the velocity of mivacurium hydrolysis increased gradually as substrate concentration increased.

At equal multiples of the K_m concentration (0.1–2), the rate of metabolism of mivacurium is about 70% that of succinylcholine. In contrast, Savarese et al. (1) noted that the hydrolysis rate of mivacurium was 88% that of succinylcholine at equal substrate concentrations (5 μM); these substrate concentrations, however, are not equal multiples of the K_m. The rate of metabolism of both drugs at any given concentration is directly related to butyrylcholinesterase activity. The estimated half-life of mivacurium increased as butyrylcholinesterase activity decreased. We speculate that the rate of hydrolysis of mivacurium by abnormal genotypes of butyrylcholinesterase will be reduced as it is with succinylcholine (5,6). Indeed, recently we compared the hydrolysis of mivacurium and succinylcholine in pooled normal plasma to that from a patient with known butyrylcholinesterase deficiency (butyrylcholinesterase activity 1200 U/L, dibucaine number 25). The hydrolysis rate of succinylcholine (20 mM) was 80.3 U/L in normal plasma and 20.0 U/L in the abnormal plasma; the hydrolysis rate of mivacurium (18 μM) was 15.7 U/L in normal plasma and 0 U/L in the abnormal plasma.

The disposition of both drugs in vivo is complicated by possible differences in the volumes of distribution, the sensitivity of the neuromuscular junction to the relaxant, and enzyme kinetics, and perhaps by alternative routes of elimination. Little has been published about the pharmacokinetics of either drug. Pharmacodynamic data from several clinical studies, however, can be used to provide some additional insights into the in vivo issues. The potency (ED_{95}) of a relaxant is related to the volume of distribution (V_d) and to the plasma concentration associated with 95% neuromuscular blockade (C_{ss95}):

$$ED_{95} = V_d \times C_{ss95} \qquad (1)$$

The ED_{95} of succinylcholine is about 300 μg/kg [Smith et al. (7) and Dr. Cook, unpublished data] and that of mivacurium is about 60 μg/kg (1,2). The molar weight of mivacurium (free base) is about threefold higher than that of succinylcholine (1029 g vs 290 g). Thus, on a molar basis the ED_{95} of succinylcholine is 0.8 μmol/kg, and that of mivacurium is 0.06 μmol/kg. If the volumes of distribution for the two relaxants were of the same order of magnitude, the plasma concentration achieved following instantaneous mixing would be about tenfold higher with succinylcholine than with mivacurium. Plasma concentrations following a bolus of mivacurium (2 × ED_{95}) are in the range of 2–10 μmol/L (2000–10,000 ng/ml) or 0.01–0.04 K_m. It is unlikely that equimolar concentrations of the two relaxants are achieved clinically, but likely that the molar concentration of succinylcholine achieved is less than the K_m. Hydrolysis of both drugs should follow first-order kinetics, and the hydrolysis of succinylcholine will be more rapid because of the higher initial concentration and differences in enzyme kinetics.

During infusions of relaxants to maintain a steady-state neuromuscular blockade, the infusion rate will equal the removal rate. At steady-state 95% neuromuscular blockade the removal rate (R) is equal to the product of clearance (Cl) and C_{ss95}:

$$R = Cl \times C_{ss95} \qquad (2)$$

Clearance is related to volume of distribution (V_d) and to the elimination half-life ($t_{1/2}$) by the expression:

$$Cl = \frac{0.693\ V_d}{t_{1/2}} \qquad (3)$$

Thus, equation 2 can be rewritten as:

$$R = \frac{0.693\ V_d}{t_{1/2}} \times C_{ss95} \qquad (4)$$

Note that $V_d \times C_{ss95}$ in equation 4 is equal to the ED_{95}. Hence,

$$R = \frac{0.693\ ED_{95}}{t_{1/2}} \qquad (5)$$

We have determined both the ED_{95} and the steady-state infusion requirements of succinylcholine and mivacurium in adults during nitrous oxide–narcotic anesthesia (2,3,8). The removal rate for succinylcholine was 88.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (0.25 $\mu mol \cdot kg^{-1} \cdot min^{-1}$), and that for mivacurium was 7.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (0.007 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). Neither tachyphylaxis nor overt signs of a phase II block were seen during the succinylcholine infusion. Using these data we estimate from equation 5 that the half-life for succinylcholine is 2.3 minutes and that for mivacurium is 5.3 minutes. The pharmacokinetic half-life of a drug can also be estimated from observations of effect (9,10). One can estimate the half-lives of succinylcholine and mivacurium from dose–duration relationships. Doubling the dose of the drug will produce a duration of action that is prolonged by the length of the elimination half-life of the drug. Data from studies in which the dose of relaxant has been doubled suggest that the half-life of succinylcholine ranges from 2 to 5 minutes and that of mivacurium from 5 to 10 minutes (1,2,9,11,12). These clinical estimates of the mivacurium half-life are in good agreement with the in vitro half-lives.

In summary, over a clinically relevant range of plasma drug concentrations and enzyme activities, the rates of hydrolysis of the two relaxants follow first-order kinetics. The combination of differences in relaxant potency and enzyme kinetics between the two relaxants is responsible for the difference of a factor of 2 or 3 in the duration of effect.

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ANESTH ANALG 1989;68:457–61

Variation in the Resting Metabolic Rate of Mechanically Ventilated Critically Ill Patients

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WEISSMAN C, KEMPER M, HYMAN AI. Variation in the resting metabolic rate of mechanically ventilated critically ill patients. Anesth Analg 1989;68:457–61.

There has been increasing interest in the nutritional support of the critically ill patient. The day-to-day variation in resting energy expenditure (REE) was studied over a 3–5-day period in 17 postoperative mechanically ventilated critically ill patients to gain insight as to how often caloric intake should be reassessed, whether changes observed over 3–5 days are of sufficient magnitude to make frequent adjustments in caloric intake, and what factors are associated with large alterations in metabolic rate. REE was measured daily for 3–5 days, and the percent variation in REE [(highest REE − lowest daily REE)/(lowest daily REE) × 100] calculated. The variation ranged from 4 to 56%, and on further analysis two distinct groups were identified, one with a mean variation of 12 ± 4% (SD) (range 4–18%) and the other with a mean variation of 46 ± 8% (range 37–56%). The former group was clinically stable, whereas the latter was not. Clinically stable patients need less frequent measurements than those who are more ill, but when designing a nutritional regimen for them, at least 20–25% should be added to the REE, 15% to account for day-to-day variation and 5–10% for activity.

Key Words: METABOLISM, METABOLIC RATE—nutritional requirements. OXYGEN—consumption.

The need to provide nutritional support to critically ill patients has become increasingly evident. Failure to provide adequate nutritional intake to these patients may result in the detrimental physiological changes associated with malnutrition, including skeletal and respiratory muscle weakness (1,2) compromised host defenses (3), and cardiac abnormalities (4). Yet designing nutritional regimens for such patients is difficult because of the complexity of their underlying disease processes and the dearth of knowledge as to their substrate and caloric requirements.

Previous observations have demonstrated the difficulty in predicting the resting energy expenditures (REE) of critically ill patients, and it has been recommended that energy expenditure be measured using indirect calorimetry (5). Other studies have observed that the total energy expenditure of critically ill patients is about 5–10% greater than the REE (6,7). This study extends these observations by examining the day-to-day variation in resting energy expenditure of critically ill mechanically ventilated patients. This is a vital issue in such patients, since they are often clinically unstable, receive large amounts of sedatives and muscle relaxants, and are febrile and septic, all situations that alter metabolic rate. It is important to ascertain the degree to which metabolic rate changes from day to day and to identify factors affecting these changes in order to address to the following questions: 1) How often should energy expenditure be reassessed? 2) Are the changes observed over a 3–5-day period of sufficient magnitude to require frequent adjustments in caloric intake? 3) What factors are associated with large alterations in metabolic rate?

In an attempt to answer these questions, we studied mechanically ventilated postoperative critically ill patients daily for 3–5 days.

Methods

Seventeen mechanically ventilated, noncomatose, postoperative critically ill patients (Table 1) located in the Surgery-Anesthesiology Intensive Care Unit (SAICU) of the Columbia-Presbyterian Medical Center were studied. They ranged in age from 18 to 95 years (mean 65 ± 20 SD years). The patients were selected as follows. Each Monday morning patients in the SAICU were reviewed by the investigators and

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Table 1. Patient Characteristics

Operative procedure	No. of patients (n = 17)	Diagnosis
Bowel resection (large and small)	9	Small bowel (n = 4) and large bowel (n = 3) obstruction, diverticulosis (n = 2)
Pneumonectomy	1	Lung cancer
Sternal wound debridement	1	Status—postcoronary artery bypass, sternal wound infection
Gastrectomy	1	Gastric cancer
Above knee amputation	1	Peripheral vascular disease
Iliac artery repair	1	Gunshot wound to abdomen
Repair of GSW to liver	1	Gunshot wound to liver
Cervical fusion; quadriplegia	1	Motor vehicle accident, cervical spine fx
Exploratory laparotomy for GSW	1	Gunshot wound to abdomen
Nutritional intake during the study period (n = 20 studies in 17 patients)		
5% dextrose	3	
TPN	9	
Enteral	1	
Enteral plus TPN	1	
5% dextrose followed by TPN	6	

GSW = gunshot wound; TPN = total parenteral nutrition.

Table 2. Metabolic Parameters in the 13 Patients Studied for at Least 4 Days (mean ± SD)

Day	Vo_2 (ml/min)	Vco_2 (ml/min)	RQ	REE (kcal/day)
1	265 ± 66	204 ± 45	0.78 ± 0.07	1749 ± 377
2	256 ± 62	199 ± 46	0.80 ± 0.05	1698 ± 338
3	252 ± 56	206 ± 52	0.82 ± 0.05	1685 ± 330
4	250 ± 54	207 ± 55	0.82 ± 0.06	1690 ± 358

a subject was chosen from those thought likely to require three or more days of mechanical ventilation. Four of the patients were studied for 3 days, eight for 4 days, and three for 5 days. One patient was studied for two 4-day periods and one for two 4- and one 5-day period. On each study day, continuous measurements of oxygen consumption (Vo_2) and carbon dioxide production (Vco_2) were performed over a 5-hour period (10:00 AM–3:00 PM) using a Horizon Metabolic Measurement Cart (Sensormedics, Anaheim, CA). In vitro studies using the method of Damask et al. (8) have demonstrated that the Horizon is able to measure Vo_2 and Vco_2 to within ±6% of predicted over the range of Fi_{O_2} of 0.21–0.60. Continuous measurements were made for 5 hours except for brief periods of endotracheal tube suctioning. To assure a constant Fi_{O_2}, the air and oxygen intakes of the Bear I and II respirators were provided with gas blended by a single Puritan Bennett AO-I air–oxygen blender (9). A log was kept of the activity states of the patients, and standardized definitions of events were used (10). Resting was defined as lying motionless with eyes open, responsive to surrounding events. At least three periods of rest were observed during each 5-hour study period. The Vo_2, Vco_2, and respiratory quotient (RQ = Vco_2/Vo_2) during these periods were averaged to determine resting levels. Resting levels were then used to calculate REE using the Weir equation (11):

$$\text{REE (kcal/day)} = (3.9 \times \text{Vo}_2 + 1.1 \times \text{Vco}_2) \times 1.44$$

The percent variation in REE was calculated as follows:

$$\frac{\text{Highest dailey REE} - \text{Lowest daily REE}}{\text{Lowest daily REE}} \times 100$$

The study was approved by the Institutional Review Board, Columbia University, Health Sciences.

Results

Resting Vo_2 ranged from 2.3 to 5.9 $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ and RQ from 0.68 to 0.95. The RQ of 0.68 was observed in a patient with ketonemia and ketonuria. Mean daily Vo_2, Vco_2, RQ, and REE are shown in Table 2. Day-to-day variation ranged from 4 to 56% with a mean of 21 ± 16% (SD). Examination of the data revealed two distinct groups (Fig. 1). In group 1 (n = 12), variation ranged from 4 to 18% (mean 12 ± 4%), while in group 2 (n = 5) it ranged from 37 to 56% (mean 46 ± 8%). Factors associated with the large variation observed in group 2 included resolution of severe sepsis, emergency surgery, and overfeeding with large carbohydrate loads (Figs. 2 and 3).

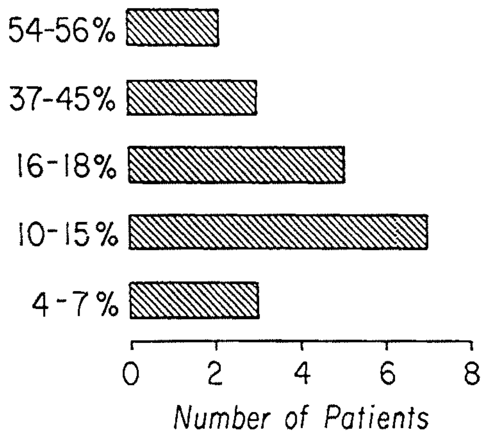

Figure 1. Distribution of day-to-day variability in critically ill patients.

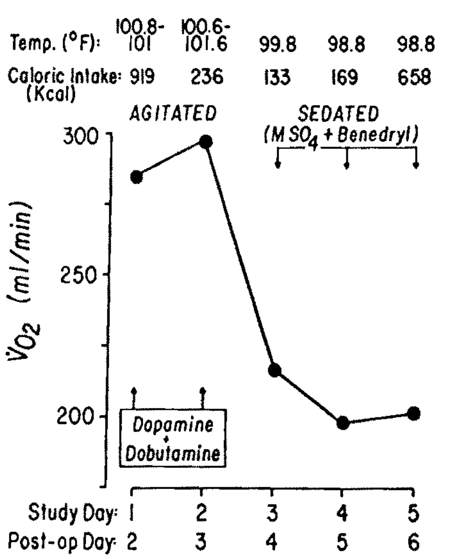

Figure 2. An example of data on a 95-year-old patient in group 2 who had undergone an emergency colectomy for a perforated colon. The large changes in REE were attributed to resolution of sepsis and fever, discontinuation of vasopressor support, and sedation of the patient.

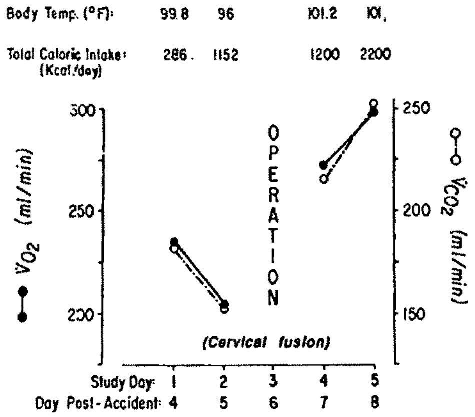

Figure 3. Data on another patient in group 2 who was a 51-year-old man with a fracture of the cervical spine. There was a large increase in energy expenditure after surgery, but, in addition, the patient was febrile and receiving parenteral nutrition. (MSO_4 = morphine sulfate).

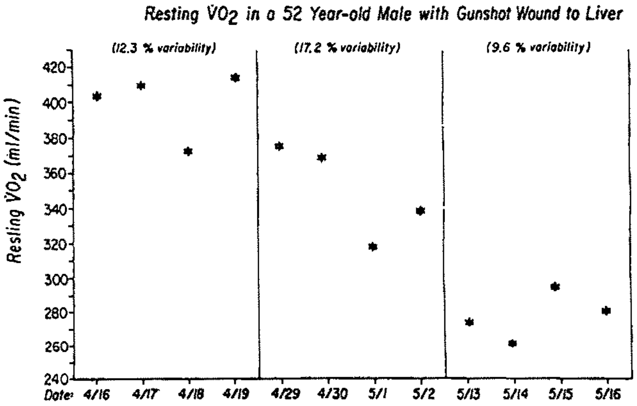

Figure 4. Data for patient who sustained a gunshot wound to the liver who was studied on the first, third, and fifth weeks of his ICU stay.

Discussion

This study quantitates the day-to-day variation in resting energy expenditure in mechanically ventilated critically ill patients. The main reason for quantitation of this variability was to aid in the design of nutritional regimens, specifically caloric requirements. In addition, this information is useful in determining how often the energy expenditure of such patients should be assessed. There were two rather distinct groups of patients (Fig. 1)—one with a mean variation in REE of 12 ± 4% (group 1), and the other with a mean variation in REE of 46 ± 8% (group 2). The distinguishing trait between the two groups was that in the latter major changes in clinical condition and therapy occurred during the study period. These changes included resolution of severe vasopressor-dependent sepsis (Fig. 2), cervical fusion surgery (Fig. 3), and feeding with large caloric and carbohydrate loads. These situations were all clinically recognizable. It thus appears that in patients who have major changes in their clinical condition, frequent (possibly daily) reassessment of metabolic rate is indicated.

In the other patients (group 1) there was a mean variation of 12% over the 3–5-day study period, but, as demonstrated in the patient whose data are shown in Figure 4, the variation over a longer period of time (5 weeks) may be greater and, more important, may vary in one direction. This patient had sustained a gunshot wound to the liver and over the ensuing 5 weeks progressively improved, becoming afebrile and less hypermetabolic. Although there was a 9–15% variation within each of the three 3–5-day periods studied, there was a significant decline in resting metabolic rate from week 1 to week 5. Therefore, it is probably reasonable to reassess caloric requirements at least every 4–5 days in patients without major changes in clinical condition or therapeutic intervention.

The observations made in group 1 also indicate that when one wishes to formulate a nutritional regimen in critically ill patients, it is prudent to administer calories in excess of measured REE to account for activity and day-to-day fluctuation in metabolic rate. Previous studies (6,7) have demonstrated that in mechanically ventilated critically ill patients similar to those studied here, the total energy expenditure over 8- and 24-hour periods is approximately 5–10% above REE. Therefore, assuming a day-to-day variability of 15%, providing nutritional intake 1.25 times measured REE will provide 1.1–1.4 times REE. The recommendation to provide at least 1.25 times measured REE is consistent with the recommendation of others (12) that critically ill patients in whom weight maintenance is the goal should receive at least 1.3 times REE. Unfortunately, the authors proposing this do not provide a rationale for their recommendations.

In addition to quantitating the day-to-day variability of the resting energy expenditure of mechanically ventilated critically ill patients, the present study also identified some of the factors that may determine day-to-day variation. The stress of surgery and sepsis is associated with an increase in metabolic rate of 5–50% (13) depending on the extent of surgery and severity of sepsis. During convalescence from such conditions, there is a gradual reduction in the hypermetabolism and hypercatabolism of stress. Similar observations were made in one of the critically ill patients (Fig. 2) in whom resolution of severe, vasopressor-requiring sepsis resulted in a decrease in metabolic rate. Conversely, when patients have a stressful event, metabolic rates increases significantly. This is illustrated in Figure 3, where, after cervical fusion, metabolic rate increased significantly. However, it is important to note that in both of these patients (Figs. 2 and 3) other factors also contributed to the changes in metabolic rate. In the patient, whose data are given in Figure 3, these included fever and the initiation of parenteral nutrition. Fever can increase metabolic rate as much as 7%/°C (14). Initiation of TPN can increase REE due to the resultant specific dynamic action of foodstuffs, which may be more marked in stressed patients (15). This effect is accentuated in septic or injured patients given TPN that contains large glucose loads with a resulting significant increase in V_{O_2} and urinary norepinephrine excretion (15). One septic patient in group 2 was being given large loads of glucose (carbohydrate calories one and a half times REE) during this study period and had a large day-to-day variability (42%).

Simultaneously occurring events that have opposite effects are also common in critically ill patients. For instance, muscle relaxants decrease V_{O_2} by 10–15% when administered to mechanically ventilated patients (16). Sedation with large doses of drugs, such as barbiturates and narcotics, is frequently used in mechanically ventilated patients. Such sedation can also decrease metabolic rate (17) and may have contributed to the decrease in metabolic rate in the patient in Figure 2. Other causes of reduced metabolic rate include hypothermia and hypothyroidism. Causes of increased metabolic rate, in addition to those already mentioned, include hyperthyroidism and catecholamine infusions (18). When analyzed as a group, the patients in this study had no significant change in REE between the first and last day of the study (Table 2). This is probably due both to the lack of rapid improvement in their general clinical condition and to the fact that there were a number of simultaneously operating factors that could alter REE. Since these factors could either raise or lower REE, the sum total change in REE is minimal.

In conclusion, the day-to-day variability in resting metabolic rate in mechanically ventilated critically ill postoperative patients studied over 3–5 days ranged from 4 to 56%. Two distinct groups of patients were identified, one with a mean variation of 12 ± 4% and the other with a mean variation of 46 ± 8%. The former was clinically stable, whereas the latter was not. The practical application of these observations means that it is prudent to consider this variability when designing nutritional regimens. Therefore, at least 20–25% (15% for variability and 5–10% for activity) should be added to the resting energy expenditure in critically ill patients similar to those studied here. More study of the changes in metabolic rate and their causes in other types of critically ill patients is needed. Also needed are studies of the degree of variability over longer time periods. In addition, it must be determined whether there are more clinical advantages to frequent adjustments in caloric intake than placing the patient on a constant nutritional regimen based on an initial metabolic measurement.

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The Effect of Sublingual Nifedipine on Coronary Venous Graft Resistance Immediately Following Cardiopulmonary Bypass

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EIDE TR, KATZ RI, POPPERS PJ. The effect of sublingual nifedipine on coronary venous graft resistance immediately following cardiopulmonary bypass. Anesth Analg 1989;68:462–6.

The purpose of this study was to determine the effects of sublingual nifedipine administered immediately after discontinuation of cardiopulmonary bypass on coronary graft resistance and systemic hemodynamics. Twenty patients were prospectively randomized into two groups; one given 10 mg sublingual nifedipine after weaning from bypass, the other given a placebo. Coronary graft blood flow was measured under blinded conditions and graft resistance calculated from measurements obtained with an electromagnetic flow probe applied directly to the graft prior to and 15 minutes after drug administration. Serum nifedipine levels were determined immediately before and 15, 30, and 60 minutes after sublingal administration. All patients receiving nifedipine had therapeutic serum levels. Graft resistance in patients given nifedipine decreased a statistically significant average of 27% and increased slightly, but not statistically significantly so, in patients given sublingual placebos. There were no differences between the two groups in cardiac index or pulmonary capillary wedge pressures. We conclude that the administration of sublingual nifedipine to patients in the immediate postbypass period results in therapeutic serum nifedipine levels and decreases coronary graft resistance without affecting cardiac performance.

Key Words: ANESTHETICS, intravenous: sufantanil. ANESTHESIA—cardiovascular. HEART—nifedipine.

Patients undergoing operative revascularization of the coronary circulation are at risk for development of intraoperative myocardial ischemia and dysfunction. Furthermore, myocardial function immediately following cardiopulmonary bypass may be compromised by coronary embolic events, inadequate graft flow, or coronary artery spasm. Nifedipine is a calcium channel blocking agent effective in relieving coronary artery spasm (1,2) and improving the ischemic myocardium (3,4) that can only be administered sublingually. It was the purpose of this study to investigate the absorption of sublingual nifedipine immediately after termination of cardiopulmonary bypass and determine its effects on coronary venous graft resistance and systemic hemodynamics.

Methods

Twenty subjects scheduled for elective coronary artery bypass grafting were enrolled in the study, which was approved by the Committee on Research Involving Human Subjects; informed consent was obtained from each patient. Patients with significantly impaired myocardial function (ejection fraction <50%, pulmonary capillary wedge pressure >15 mm Hg) or >70 years were excluded from the study. Premedication consisted of morphine 0.1 mg/kg I.M. and lorazepam 2 mg orally was given 1 hour prior to surgery. All cardiac medications (beta-adrenergic inhibitors, nitrates, and calcium channel blockers) that the patient was receiving were continued.

Routine monitoring included electrocardiogram plus, pulse oximetry, and measurement of systemic arterial blood pressure. Intravenous radial and pulmonary artery catheters were inserted.

General endotracheal anesthesia was induced with sufentanil 15.0 μg/kg and tracheal intubation facilitated with the administration of pancuronium and vecuronium. After induction, a Foley catheter, an esophageal temperature probe, an oro-gastric tube, and an end-tidal carbon dioxide probe were added. A continuous computerized patient data management system (Siemens Sirecust) was used to continuously record heart rate and systemic and pulmonary artery

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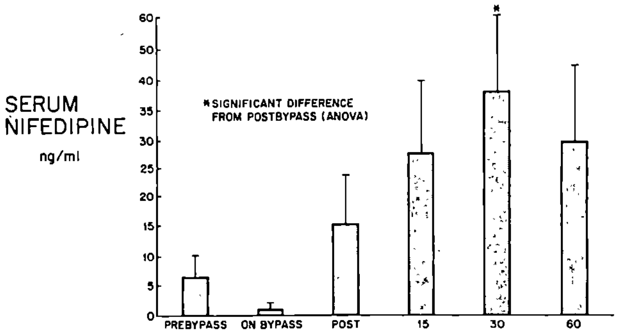

Figure 1. Serum nifedipine levels in patients given sublingual nifedipine. The prebypass, bypass, and postbypass levels were measured in 9 patients from groups A *and* B who were receiving nifedipine chronically. The 15, 30, and 60 min levels are in group A patients only. (mean ± SEM)

pressures. Cardiac output by thermodilution, as the average of three measurements at each point, was determined with use of the American Edwards cardiac output monitor.

After completion of coronary artery grafting, separation from extracorporeal circulation was facilitated with the infusion of dobutamine (3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). No vasodilators nor calcium were administered.

Patients were randomized at that point to be given sublingually a capsule containing nifedipine (10 mg; group A) or a placebo (group B). The anesthesiologist and surgeon were unaware of the contents of the capsule.

The flow in each venous graft 5 minutes after termination of cardiopulmonary bypass was determined by the surgeon using an electromagnetic blood flow probe (Cliniflow II, Carolina Medical Electronics) and resistance calculated with use of simultaneous measurements of diastolic blood pressure and pulmonary capillary wedge pressure. Measurement of graft flow and calculation of graft resistance were repeated 15 minutes after drug administration. The flow probe was applied to each graft, zeroed after each measurement in blood by the surgeon, and considered to be a steady measurement for at least 5 seconds on each graft. The stated error of the device is ±3.0%.

Arterial blood samples were collected in aluminum foil wrapped test tubes 10 minutes prior to bypass (prebypass), 30 minutes after the start of bypass, immediately after bypass, and then 15, 30, and 60 minutes thereafter. The serum was separated by centrifugation under light controlled conditions and frozen until determination of nifedipine levels by high pressure liquid chromatography (National Medical Services, Willowbrook, PA). The sensitivity of the method was such that concentrations <10 ng/ml could not be measured accurately. Levels of nifedipine in the range of 25–100 ng/ml were considered to be therapeutic (5).

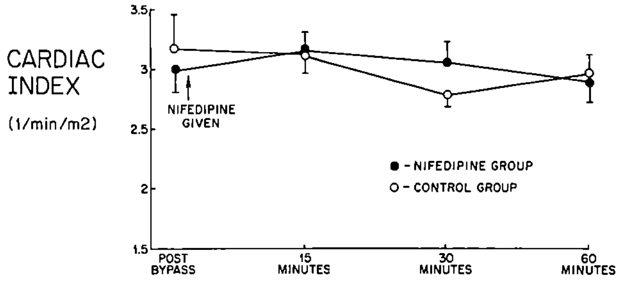

Figure 2. Cardiac Index after cardiopulmonary bypass. (mean ± SEM) ANOVA - differences not significant.

Coronary graft resistance was calculated as the diastolic blood pressure minus the pulmonary capillary wedge pressure divided by the coronary blood flow in milliliters per minute. Calculations of systemic vascular resistance and cardiac index were performed with standard fomulae.

Paired Student's *t* test or ANOVA was used, where appropriate, to determine whether differences between the two groups were statistically significant. A *P* value of <0.05 was considered statistically significant.

Results

Randomization assigned 12 patients to group A (10 mg nifedipine), which consisted of 9 men and 3 women with a mean age of 61 ± 2 years. The eight patients in group B (no nifedipine) contained six men and two women with a mean age of 60 ± 4 years. In 2 of the 12 patients of group A, serum levels of nifedipine were not measured because of technical difficulties. Four of the 12 patients in group A and 5 of the 8 patients in group B were taking nifedipine chronically and received their preoperative dose approximately 4 hours prior to cardiopulmonary bypass.

In no patient was the serum nifedipine level within the therapeutic range 10 minutes prior to cardiopulmonary bypass. The administration of sublingual nifedipine to patients in group A resulted in therapeutic serum levels measured 15, 30, and 60 minutes after (Fig. 1). The peak mean serum concentration occurred at 30 minutes.

Nifedipine had no significant effect on cardiac index (Fig. 2) or pulmonary capillary wedge pressure (Fig. 3) when compared with the postbypass levels. We observed a tendency for the systemic mean arterial blood pressure (Fig. 4) to decrease (5–10 torr) after nifedipine was given. However, these changes

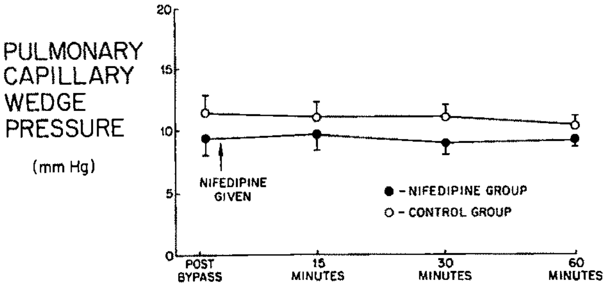

Figure 3. Pulmonary capillary wedge pressure after cardiopulmonary bypass. (mean ± SEM) ANOVA - differences not significant.

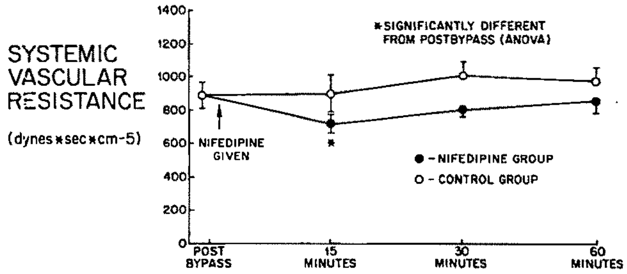

Figure 5. Systemic vascular resistance after cardiopulmonary bypass. (mean ± SEM)

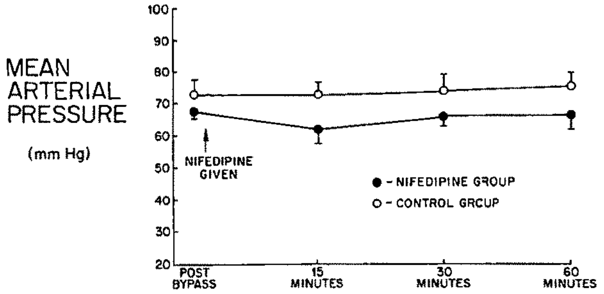

Figure 4. Mean arterial pressure after cardiopulmonary bypass. (mean ± SEM) ANOVA - differences not significant.

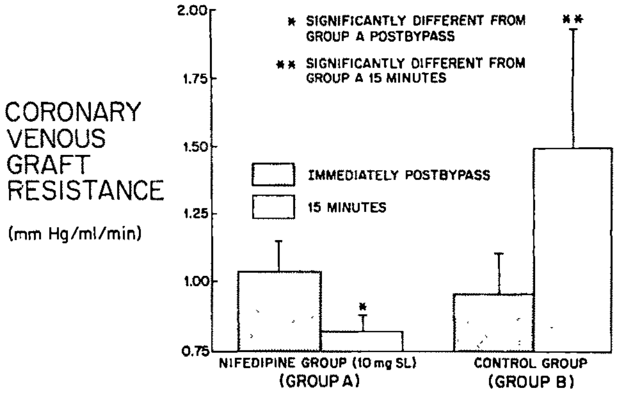

Figure 6. Coronary Venous Graft Resistance five minutes after cardiopulmonary bypass and fifteen minutes after nifedipine 10 mg SL (group A) and a control group (group B). (mean ± SEM)

did not achieve statistical significance. The systemic vascular resistance (Fig. 5) in group A was approximately 10–20% less than that in group B at 15, 30, and 60 minutes. These differences reached statistical significance at 15 minutes.

Venous graft resistance (Fig. 6) in group A decreased 27% when measured at 15 minutes after the sublingual administration of nifedipine ($P < 0.05$). There was a trend for venous graft resistance to increase in patients not given nifedipine (group B). The difference in graft resistance between groups A and B was statistically significant at 15 minutes ($P < 0.05$).

Discussion

Our data indicate that nifedipine (10 mg) given by sublingual administration after termination of extracorporeal circulation results in therapeutic blood levels with a peak mean blood concentration of drug at 30 minutes. This dose of nifedipine had no untoward hemodynamic effects and resulted in a 27% decrease in coronary venous graft resistance.

The sublingual route of administration of nifedipine produces rapid pharmacodynamic effects (6–9,10,11). Indeed, the absorption of nifedipine after sublingual administration results in detectable serum concentrations more rapidly than after oral administration (6). Nifedipine levels were assayed in the current study to demonstrate that sublingual nifedipine is readily absorbed in the immediate post-cardiopulmonary bypass period. There was large inter-patient variability in nifedipine serum levels, as also noted in studies of nifedipine pharmacokinetics in healthy volunteers (6,12). We postulate that the sub-therapeutic nifedipine levels found prior to cardiopulmonary bypass in this group of patients receiving nifedipine chronically was secondary to delayed gastric emptying and decreased absorption of the capsule in this pre-surgical group. Alternatively, the need for administering a nifedipine premedication closer to the induction of anesthesia may exist.

Studies correlating serum nifedipine levels to pharmacodynamic effects have been conflicting. One study that compared nifedipine serum levels after oral and sublingual administration found an inverse relationship between blood levels of drug and diastolic blood pressure (12). This is in contrast to another study that found no correlation between drug levels and blood pressure (13). We found no statistically significant change in cardiac index or pulmonary capillary wedge pressure after the administration of sublingual nifedipine. Mean systemic arterial pressure and systemic vascular resistance tended to decrease after nifedipine administration, however, except for the decrease in systemic vascular resistance at 15 minutes, these did not achieve statistical significance.

Coronary artery spasm has been well described as the etiology of variant angina (1,2,14) and may be implicated in other forms of ischemic heart disease. Coronary arterial vasospasm immediately after surgical revascularization has resulted in intraoperative ischemia (12,15,16) and perioperative cardiac arrest (17,18). Manipulation of the venous graft, alkalosis, alpha-adrenergic agents, and thromboxane A_2 released from platelets are believed to provoke spasm (19,20–22). Nifedipine, a calcium channel blocking agent currently used to treat variant as well as exercise-induced angina (4), may be considered an appropriate form of intraoperative therapy when spasm of the coronary circulation is suspected.

Sublingual nifedipine has also been shown to be beneficial in management of acute myocardial infarction (3), perhaps because of afterload reduction and a concomitant decrease in myocardial oxygen consumption, although coronary artery dilation as well as a direct myocardial metabolic effect may be also involved. One study (23) found that an intracoronary injection of nifedipine at a dose that caused no systemic hemodynamic changes had a metabolic effect independent of reduced afterload in relieving myocardial ischemia. Another investigation suggested alleviation of ischemic symptoms partly due to afterload reduction, an increase in collateral blood flow, and a possible dilation of stenotic portions of coronary arteries (9).

Our study investigated graft resistance as a marker for a nifedipine effect on the coronary circulation during the immediate postbypass period. Although our study cannot comment on the total coronary circulatory effects of nifedipine (i.e., grafts plus native circulation and collaterals), we can conclude that the sublingual administration of nifedipine (10 mg) resulted in therapeutic serum concentrations that decreased the resistance in coronary venous grafts. Furthermore, although some mild decreases of systemic mean arterial blood pressure (which were not statistically significant) were observed, no adverse changes were noted in cardiac index or pulmonary capillary wedge pressure.

With the current body of literature implicating spasm as a significant contributing factor in the development of intraoperative and postoperative ischemia, it, therefore, seems reasonable on the basis of our results to consider the administration of sublingual nifedipine as a possible therapeutic modality when intraoperative myocardial ischemia is present and vasospasm of the coronary circulation is suspected. Further study, however, will be necessary to determine whether nifedipine prevents ischemia in the postbypass period.

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Hemodynamic Effects of Dobutamine in Patients Following Mitral Valve Replacement

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SCHWENZER KJ, MILLER ED Jr. Hemodynamic effects of dobutamine in patients following mitral valve replacement. Anesth Analg 1989;68:467–72.

Mitral valve replacement is frequently complicated by a low cardiac output syndrome and elevated pulmonary arterial pressures. In the present study, we used dobutamine to increase cardiac index and measured the pulmonary hemodynamic effects in 10 patients with increased pulmonary vascular tone following mitral valve replacement. Using increasing doses of dobutamine up to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, we observed a statistically significant increase in mean cardiac index (from 2.39 ± .14 $liters \cdot min^{-1} \cdot m^{-2}$ to 3.52 ± .33, $P < 0.01$) and mean heart rate (from 71.6 ± 5.2 $beats \cdot min^{-1}$ to 84.3 ± 8.1, $P < 0.01$). This was associated with stable mean systemic arterial pressures and mean pulmonary arterial pressures. Both mean systemic and pulmonary vascular resistances decreased significantly (from 1210 ± 99 $dynes \cdot sec \cdot cm^{-5}$ to 809 ± 90 [$P < 0.01$], and from 195.9 ± 30.6 $dynes \cdot sec \cdot cm^{-5}$ to 129.4 ± 41.2 [$P < 0.01$] respectively) with dobutamine. Intrapulmonary shunt flow increased significantly in the five patients studied. Though increases in heart rate and pulmonary shunt flow may limit its use, dobutamine increases cardiac output and decreases pulmonary vascular resistance in patients with increased pulmonary arterial pressure following mitral valve replacement.

Keys Words: LUNG, PULMONARY HYPERTENSION, pulmonary circulation. ANESTHESIA—cardiovascular. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dobutamine.

Mitral valve replacement is frequently complicated by a postoperative low cardiac output syndrome. Vasoactive agents are not uncommonly needed in such patients. Comparative studies suggest dobutamine has many advantages over isoproterenol (1,2) and dopamine (3–5) by having a predominant beta-1-receptor-mediated inotropic action with weak chronotropic and peripheral effects. Although the systemic effects of dobutamine have been well studied in patients, the effect on the pulmonary vasculature remains controversial. Many investigators (1,3–7) describe significant reductions in pulmonary vascular resistance with no change in mean pulmonary arterial pressure using dobutamine for inotropic support. However, the effect of dobutamine in patients with increased pulmonary arterial pressure following mitral valve surgery is unclear. DiSesa and colleagues (8), using 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dobutamine in 6 patients following mitral valve replacement surgery, found no significant change in either mean pulmonary arterial pressure nor pulmonary vascular resistance. In contrast, Tyden and Nystrom (9) found significant pulmonary vasoconstriction following valve replacement surgery using a mean dobutamine dose of 7.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Dobutamine is regularly used in our surgical intensive care unit to provide inotropic support following mitral valve replacement in patients with elevated mean pulmonary artery pressures. If dobutamine is a pulmonary vasoconstrictor, it would be detrimental in this patient population. Therefore, the purpose of this study was to evaluate the effects of a range of dobutamine doses on pulmonary artery pressure, pulmonary vascular resistance, and right-to-left intrapulmonary shunt flow following mitral valve replacement in patients requiring postoperative inotropic support.

Methods

Following institutional approval and informed consent, ten patients undergoing cardiac operations at

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Table 1. Preoperative Patient Data

Pt #	Age/Sex	BSA (m^2)	Diagnosis	Operation	Preoperative Mean PAP (mm Hg)
1	64 M	1.7	MS	MVR	300
2	66 M	2.06	AS/MR/TR	AVR/MVR/TVA	50
3	57 F	1.72	MS	MVR	27
4	70 F	1.57	MS/MR/TR	MVR/TVA	19
5	63 M	2.24	MR	MVR	47
6	55 F	1.77	MR/TR	MVR/TVR	NA
7	53 M	1.69	MR	MVR	NA
8	53 F	1.5	MR/TR	MVR/TVA	50
9	57 F	1.63	MS/MR	MVR	45
10	38 M	2.42	MR	MVR	NA

MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation; AS, aortic stenosis; NA, information not available; BSA, body surface area; MVR, mitral valve replacement; TVR, tricuspid valve replacement; TVA, tricuspid valve annuloplasty; AVR, aortic valve replacement; PAP, mean pulmonary artery pressure.

the University of Virginia Medical Center were studied. The patient population is described in Table 1. No changes were made in the usual anesthetic, surgical, cardiopulmonary bypass, or surgical intensive care unit routine. Preoperatively, a flow-directed pulmonary artery thermodilution catheter was inserted under local anesthesia to measure pulmonary arterial and right atrial pressures and cardiac output by the thermodilution technique. Systemic arterial pressure was measured and blood samples obtained using a 20 gauge catheter inserted percutaneously into a radial artery. Prior to closure of the chest, a catheter was inserted into the left atrium via the right pulmonary vein in seven patients. The following variables were measured at end-expiration using a calibrated strip chart recorder: heart rate (HR); mean (MAP), systolic, and diastolic arterial pressures; mean (PAP), systolic, and diastolic pulmonary arterial pressures; left atrial pressure (LAP); and right atrial pressure (CVP). Cardiac output was measured in triplicate. In the three patients without a left atrial catheter, pulmonary capillary wedge pressure (PCWP) was monitored.

Cardiac index (CI) was calculated by dividing the cardiac output by the body surface area. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) in dyns·sec·cm^{-5} were calculated from the formulas:

$$\text{SVR} = \frac{(\text{MAP} - \text{CVP})}{\text{CO}} \times (80)$$

$$\text{PVR} = \frac{(\text{PAP} - \text{LA [or PCWP]})}{\text{CO}} \times (80)$$

The study took place between 12 and 18 hours after the end of the operation, when the rectal temperature was greater than 36.5°C. Any intravenous cardioactive drugs were discontinued. All patients had been sedated with morphine sulfate (1–4 mg intravenously). Following baseline measurements, a continuous infusion of dobutamine, 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was begun and increased by 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 20 minutes to a final concentration of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Hemodynamic measurements were recorded 15 minutes after starting 5, 7.5, and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All doses were given as indicated unless heart rate increased to more than 20% of control, mean systemic arterial pressure increased to more than 20% of control, or ventricular ecotopy increased by more than five ectopic beats per minute over baseline levels.

Arterial blood gas tensions were measured prior to and at the conclusion of the study. In five patients samples of mixed venous blood were taken from the distal lumen of the pulmonary artery catheter. Right to left intrapulmonary shunt was calculated according to the classical mixing equation, which assumes the partial pressure of oxygen in end capillary blood (Pc_{O_2}) is equal to the partial pressure of oxygen in the alveolus (PA_{O_2}), which is derived from the alveolar gas equation

$$Q_S/Q_T(\%) = CcO_2 - CaO_2/CcO_2 - CvO_2$$

where CaO_2 = arterial oxygen content (ml O_2·100cc $blood^{-1}$), CvO_2 = mixed venous oxygen content, and CcO_2 = end capillary oxygen content.

Statistical analysis using ANOVA was done using each patient's baseline as his control. All data were expressed as mean ± standard error of the mean (SEM).

Results

The hemodynamic effects of dobutamine at the three dosages are shown in Table 2. Cardiac index showed a significant stepwise increase from 2.39 ± .14 liters·min^{-1}·m^{-2} to 3.51 ± .23 ($P < 0.01$) with graded

Table 2. Hemodynamic Effects of Dobutamine

Dobutamine	0	5 μg·kg^{-1}min^{-1}	7.5 μg·kg^{-1}min^{-1}	10 μg·kg^{-1}min^{-1}
CI (liters·min^{-1}m^{-2})	2.39 ± .14	3.00 ± .18^{a}	3.51 ± .23^{a,c}	3.52 ± .33^{a}
HR (beats/min)	71.6 ± 5.2	84.9 ± 5.9^{a}	83.4 ± 6.6^{a}	84.3 ± 8.1^{a,c}
MAP (mm Hg)	74.4 ± 2.5	74.5 ± 2.7	75.1 ± 2.7	73.4 ± 3.4
CVP (mm Hg)	11.7 ± 1.49	10.3 ± 1.18	9.86 ± 1.68^{b,d}	9.0 ± 2.24^{b}
SVR (dyne·sec·cm^{-5})	1210 ± 99	993 ± 93^{a}	866 ± 84^{a,d}	809 ± 90^{a}
PA (mm Hg)	27.8 ± 2.4	27.2 ± 2.0	29.0 ± 2.9	26.2 ± 3.7
LA or PCWP (mm Hg)	18.11 ± 2.0	17.0 ± 1.66	17.43 ± 2.0	16.8 ± 2.67
PVR (dyne·sec·cm^{-5})	195.9 ± 30.6	165.2 ± 34.7^{b}	159.8 ± 39.7^{a}	129.4 ± 41.2^{a}

Values are mean ± SEM. Comparisons by ANOVA and Duncan's Multiple Range Test.

[a] $P < 0.1$ compared to baseline.

[b] $P < 0.5$ compared to baseline.

[c] $P < 0.1$ compared to previous dose.

[d] $P < 0.05$ compared to previous dose.

CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; SVR, systemic vascular resistance; PA, mean pulmonary artery pressure; LA, mean left atrial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

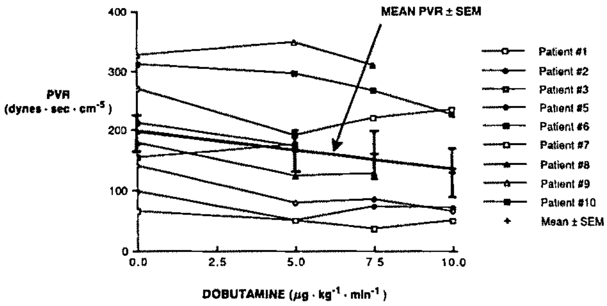

Figure 1. Individual and mean PVR data.

doses of dobutamine up to a dose of 7.5 μg·kg^{-1}·min^{-1}. No further increase was seen at 10 μg·kg^{-1}·min^{-1}. There was no change in preload, with a stable left atrial pressure or pulmonary capillary wedge pressure. Systemic and pulmonary vascular resistances dropped significantly from 1210 ± 99 dyns·sec·cm^{-5} to 809 ± 90 ($P < 0.01$) and from 195.9 ± 30.6 dyns·sec·cm^{-5} to 129.4 ± 41.2 ($P < 0.01$) respectively at a dose of dobutamine of 10 μg·kg^{-1}·min^{-1}. The individual and mean PVR data are plotted (Fig. 1). PVR could not be determined in Patient #4 due to technical difficulties with the pulmonary artery catheter. These hemodynamic changes were not associated with any significant change in mean arterial pressure, mean pulmonary arterial pressure, and mean pulmonary driving force (PAP-LAP). Dobutamine increased PAP in two patients and did not change PVR though CI increased and SVR decreased (See Table 3).

The increase in cardiac index was associated with a significant rise in heart rate from 71.6 ± 5.2 beats·min^{-1} to 84.3 ± 8.1 ($P < 0.01$). Because of the exclusion criteria only five patients were studied at the 10 μg·kg^{-1}·min^{-1} dose. The dobutamine infusion was stopped because of excessive tachycardia in 4 patients. The fifth patient had increased ventricular ectopy with two unsustained runs of ventricular tachycardia necessitating stopping the dobutamine infusion prior to giving the highest dose. With discontinuation of dobutamine, all of the arrhythmias subsided. Aside from these drug-induced arrhythmias, no side effects were observed.

Additional postoperative findings are outlined in Table 4. Patient #5 was receiving a continuous infusion of lidocaine at 2 mg·min^{-1} for ventricular ectopy. This infusion was not discontinued during the study period. None of the other patients were receiving any other intravenous drugs. Patients #5 and #7 were being atrio-ventricularly sequentially paced. Five patients had atrial fibrillation, one a nodal rhythm and two a normal sinus rhythm. Six of the patients were receiving intermittent positive pressure ventilation via an endotracheal tube. The others were breathing spontaneously with supplemental oxygen.

Arterial blood gas analysis tensions stable oxygenation and ventilation (Table 5). No patient had hypoxia, hypercarbia, or hypocarbia. Intrapulmonary shunt increased in all five patients studied from a baseline of 9.45 ± 3.95 percent to a final fraction of 18.35 ± 8.37% ($P < .05$).

Discussion

In the present study, dobutamine was used to increase cardiac output in patients with increased pulmonary vascular tone who had undergone mitral valve replacement.

Following mitral valve replacement surgery, patients often need inotropic support due to low cardiac output. Secondary to longstanding pulmonary hypertension, these patients often have elevated pulmonary artery pressures. Since data on the effects of dobutamine in these patients are scant and contradictory, we studied the effects of increasing concentra-

Table 3. Data from Patients #9 and #10

	Baseline Patient #9	Dobutamine 7.5 $\mu g \cdot kg^{-1} min^{-1}$	Baseline Patient #10	Dobutamine 5 $\mu g \cdot kg^{-1} min^{-1}$
CI (liters·min^{-1} m^{-2})	2.1	3.65	2.3	3.03
HR (beats/min^{-1})	60	100	75	102
MAP (mm Hg)	74	86	72	72
PAP (mm Hg)	27	32	29	32
PCWP (mm Hg)	13	13	18	16
CVP (mm Hg)	11	8	15	15
SVR (dyne·sec·cm^{-5})	1474	1049	826	625
PVR (dyne·sec·cm^{-5})	327	309	155	175

Table 4. Postoperative Data

Pt #	Mean PAP (mm Hg)	PVR (dyne·sec·cm^{-5})	Rhythm/Rate	Treatment
1	21	461	SR/80 with APC's	N
2	30	99	Nodal/58	N
3	25	213	AF/80	N
4	21	NA	AF/95	N
5	32	141	AVP/94	Lidocaine
6	44	311	AF/50	N
7	17	66	AVP/88	N
8	32	180	AF/75	N
9	27	327	AF/60	N
10	29	155	SR/75	N

SR, sinus rhythm; AF, atrial fibrillation; AVP, atrio-ventricular pacing; N, none; NA, information not available.

Table 5. Arterial Bood Gas Tensions

			Before Dobutamine			During Final Dobutamine Dose		
Pt #	Mode of Ventilation	F_iO_2	pH	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)	pH	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)
1	IPPV	0.3	7.37	41	83	7.49	37	62
2	FT/NP	0.4	7.41	42	80	7.44	36	94
3	IPPV	0.5	7.42	43	89	7.42	43	89
4	IPPV	0.6	7.41	41	85	7.44	38	67
5	NP	0.36	7.44	37	122	7.41	39	89
6	IPPV	0.5	7.37	40	168	7.40	40	155
7	IPPV	0.4	7.40	41	168	7.39	46	189
8	IPPV	0.4T	7.41	40	156	7.41	39	147
9	FT	0.5	7.43	41	125	7.43	44	80
10	NP	0.36	7.32	42	161	7.30	45	155

Arterial blood gas tensions revealed stable oxygenation and ventilation. Six of the patients were receiving intermittent positive pressure ventilation (IPPV) via an endotracheal tube. The others were breathing spontaneously receiving supplemental oxygen via a face tent (FT) and/or nasal prongs (NP).

tions of dobutamine in patients following mitral valve replacement.

As expected, dobutamine infusion increased cardiac output. The cause, however, was multifactorial. Consistent with hemodynamic responses in other patient populations, the combined effect of dobutamine on heart rate, preload, afterload, and contractility increased CO. We found systemic vascular resistance decreased while heart rate increased. By maintaining left and right ventricular filling pressures systemic blood pressure remained stable. In the present study pulmonary artery pressures remained stable as pulmonary vascular resistance decreased significantly to accomodate the increased blood flow caused by dobutamine.

The mechanism of this apparent afterload reducing effect of dobutamine is not fully understood. Although Robie (10) and Mikulic (3) and their colleagues isolated alpha-receptor-mediated activity in the systemic circulation, the predominant adrenergic effect of dobutamine in the intact organism is on the beta-adrenergic receptor.

Robie's group, using a canine denervated hind limb preparation, demonstrated effects of dobutamine on both alpha and beta receptors. Using low-dose dobutamine, a weak vasoconstrictor effect was seen. However, the beta-receptor-mediated action predominated, resulting in systemic vasodilation. They postulated that the decrease in systemic vascular resistance coupled with the increase in myocardial contractile force accounted for the increased cardiac output produced by dobutamine.

Mikulic et al., on the other hand, believed the decrease in systemic vascular resistance seen with dobutamine to be due to autoregulation with withdrawal of sympathetic vascular tone as cardiac output increases. Measuring human forearm blood flow with venous occlusion plethysmography, they failed to demonstrate a predominant direct vasodilating effect with dobutamine at doses corresponding to a systemic dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Though the present study failed to determine if the ability of dobutamine to decrease systemic vascular resistance is via direct activation of beta-adrenergic receptors or via an indirect release of sympathetic tone, the effect of dobutamine on the peripheral circulation can be dramatic and systemic blood pressure can decrease if adequate preload is not maintained (8,11,12).

Both alpha- and beta-adrenergic receptors are present in the pulmonary vascular bed of many species of animals, including humans (13). Because the beta-receptor-mediated activity of dobutamine exceeds its alpha-receptor-mediated activity in the systemic circulation, one might expect similar actions on the pulmonary vasculature. This may result in a decreased pulmonary vascular resistance. Such a decrease in vascular resistance was seen in the present study, as well as in others (1,3–7). Therefore, biventricular unloading can contribute to improved cardiac output in patients after mitral valve replacement.

The question often raised is how much of the reduction in pulmonary vascular resistance associated with dobutamine is due to a direct effect of on the pulmonary vessels and how much is due to the increase in cardiac output. Furmann et al. (14) inhibited hypoxic pulmonary vasoconstriction with dobutamine in pigs. Perhaps through beta-mediated-adrenergic receptors, dobutamine opened capillary networks that were previously vasoconstricted. If this is the case, the increase in pulmonary shunt flow seen in the present and other studies (15) may be evidence of a direct vasodilating effect. This is contrary to the study by Lejeune and colleagues (16) using a hypoxic pulmonary vasoconstriction model in dogs. They also demonstrated inhibition of hypoxic pulmonary vasoconstriction with dobutamine. This was contributed to the change in cardiac output because when cardiac output was held constant, no direct pulmonary vasodilating properties from dobutamine were seen. Of interest is that in their control, normoxic animals, pulmonary vascular resistance did not change with dobutamine, even though systemic vascular resistance decreased significantly. In fact, they demonstrated a significant increase in pulmonary artery pressures with dobutamine. Alpha-adrenergic-mediated receptors may predominate in the canine pulmonary circulation and account for this failure to vasodilate with dobutamine initially. In the present study two patients behaved similarly with increasing concentrations of dobutamine. Patients 9 and 10 (Table 3) had the predictable systemic responses to dobutamine; increases in cardiac index and heart rate and a decrease in systemic vascular resistance. However, the mean pulmonary arterial pressures increased in these two patients as dobutamine appeared to vasoconstrict the pulmonary bed, as with Lejeune's dogs. These two patients were among the patients with the highest starting PVR. Tyden and Nystrom (9) observed a similar effect with dobutamine in 12 patients following valvular surgery. This unpredictable pulmonary vasoconstriction emphasizes the need for serial hemodynamic monitoring when using dobutamine in patients with elevated pulmonary vascular tone.

The chronotropic effects of dobutamine are also noteworthy. The present study documented the increase in heart rate frequently seen with dobutamine. The degree of tachycardia appears to be less, however, with dobutamine than with isoproterenol and dopamine (6,9,17), although caution must still be exercised. A modest increase in heart rate can improve cardiac output, but a large increase may contribute to excessive myocardial work (18). The arrhythmogenic potential of dobutamine is also less than with dopamine and isoprenaline (6). However, arrhythmias can occur and may limit the clinical usefulness of dobutamine.

Following mitral valve replacement patients with increased pulmonary vascular tone frequently need inotropic support. Though increases in heart rate and pulmonary shunt flow may limit its use, dobutamine increases cardiac output and decreases pulmonary vascular resistance. This study emphasizes the importance of serial hemodynamic monitoring in patients with low-output syndrome following mitral valve replacement

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Effects of Diazepam and Flumazenil on Sedation and Hypoxic Ventilatory Response

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MORA, CT, TORJMAN, M, WHITE, PF. Effects of Diazepam and Flumazenil on Sedation and Hypoxic Ventilatory Response. Anesth Analg 1989;68:473–8.

We evaluated the effects of a benzodiazepine antagonist, flumazenil (Ro 15-1788), 1 mg intravenous, on the hypoxic ventilatory response in 10 healthy patients who had received diazepam 0.97 ± 0.34 mg/minute (mean ± SD) for sedation during minor operative procedures. When assessed using a sedation analog scale, flumazenil significantly decreased diazepam-induced sedation. In only two of the five patients with evidence of diazepam-induced depression of the ventilatory response to hypoxia was there significant reversal of this depression after flumazenil administration. Finally, patients in whom the duration of sedation with diazepam was shorter (78 ± 14 minutes) had a significantly greater decrease in the slope of their hypoxic ventilatory response curve (1.3 ± 0.8 $L \cdot min^{-1} \cdot \%sat^{-1}$ [−43% from baseline]) than did patients with longer sedation times (145 ± 37 minutes duration; 2.0 ± 0.8 $L \cdot min^{-1} \cdot \%sat^{-1}$ [−5% from baseline]). These data suggest that flumazenil, 1 mg intravenous, is only partially effective in reversing diazepam-induced depression of hypoxic ventilatory drive and that tolerance may develop to the respiratory depressant effects of diazepam.

Key Words: ANTAGONISTS, MISCELLANEOUS—benzodiazepines, flumazenil. HYPNOTICS, BENZODIAZEPINES—diazepam.

Benzodiazepines are widely used for sedation during diagnostic procedures. Controversy exists regarding the respiratory depressant effects of sedative and hypnotic doses of benzodiazepines. Although studies (1–14) designed to assess the effects of diazepam on ventilatory function have yielded conflicting results, the respiratory response to diazepam appears to be affected by the dose and rate of drug administration, as well as by methodologic, environmental, and individual patient factors. Despite marked variability in the respiratory response to diazepam (4,12,13), large bolus (hypnotic) doses of diazepam produce significant depression of the ventilatory response to carbon dioxide (CO_2) (8,10). Although some investigators (1,2,6,11) have reported that CO_2 responsiveness is not affected by sedative doses of diazepam, others (3,5,7,9,14) have demonstrated that even premedicant doses of diazepam can depress respiratory drive.

Knill and Gelb (15) suggested that measuring the ventilatory responses to isocapnic hypoxia was a more sensitive method to assess the respiratory depressant effects of anesthetics than the hyperoxic hypercapnic technique. In volunteers, sedative doses of benzodiazepines have been reported to significantly depress hypoxic ventilatory responsiveness (14,16). We designed a study to assess the effects of diazepam and flumazenil (Ro 15-1788), a benzodiazepine antagonist, on the hypoxic ventilatory response in patients undergoing minor surgical procedures.

Methods and Materials

Ten healthy, consenting, unpremedicated adults undergoing minor surgical (e.g., hemorrhoidectomy) or diagnostic (e.g., colonoscopy) procedures requiring intravenous (iv) sedation were studied according to a protocol approved by the local Institutional Review Board.‡ All subjects fasted for 12 hours prior to their

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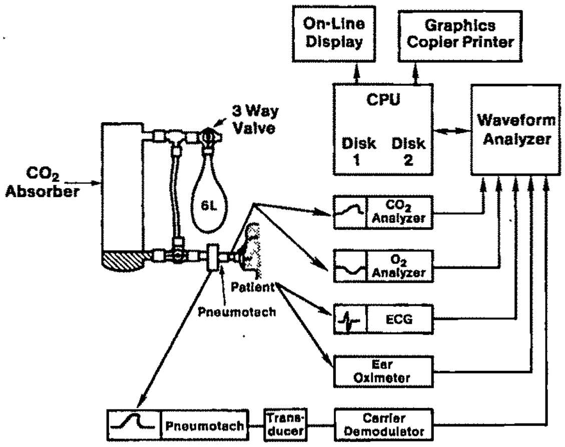

Figure 1. Schematic representation of the respiratory apparatus and monitors used to assess ventilatory response to hypoxia.

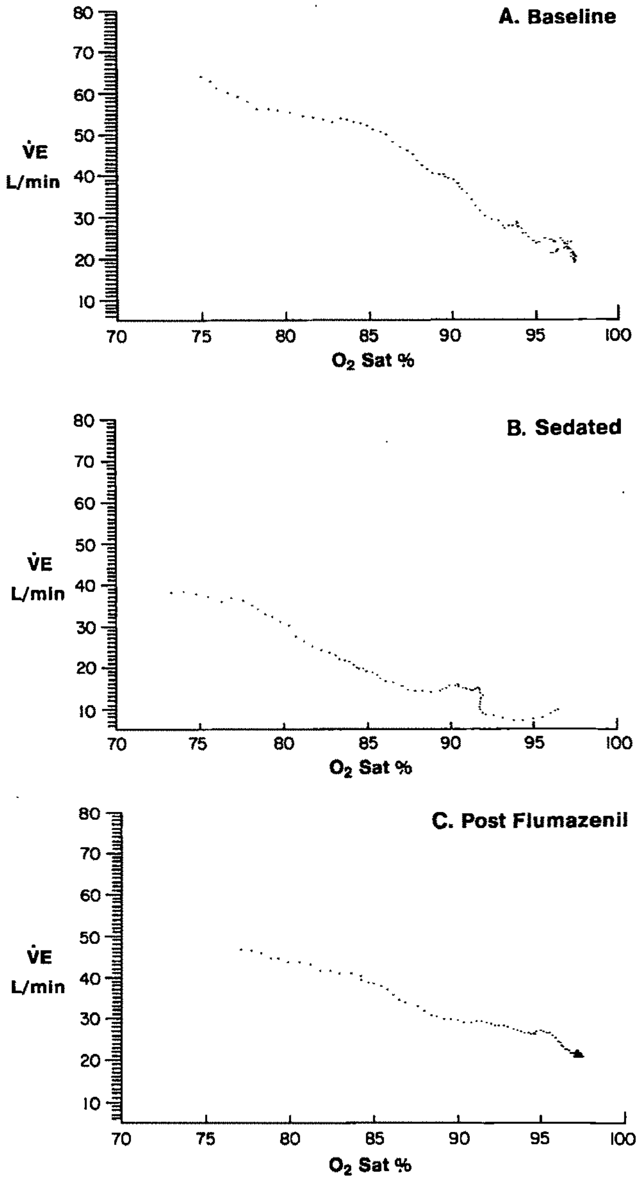

Figure 2. Hypoxic response curves in patient no. 1 demonstrating the relationship between the change in oxygen saturation (%) and minute ventilation ($L \cdot min^{-1}$). A, baseline study; B, after diazepam sedation; and, C, after flumazenil administration.

procedures. Patients with a history of pulmonary disease, drug, or alcohol abuse, as well as those taking benzodiazepines were excluded.

One hour before their elective procedure, patients were asked to assess their level of sedation with the use of a 100 mm linear analog scale (0 = awake/alert to 100 = unresponsive/sleeping). The patient's degree of sedation was also evaluated by an observer using a 5-point scale, with 1 = awake and alert, 2 = lethargic, 3 = responds to verbal stimulation, 4 = responds to tactile stimulation, and 5 = unresponsive. Baseline ventilatory studies were performed according to the method described by Rebuck and Campbell (17). The technique used for evaluating the ventilatory response to hypoxia directly relates changes in minute ventilation ($\dot{V}_E$) to changes in arterial oxygen saturation (O_2 sat.).

All respiratory studies were performed in the pulmonary function laboratory at Thomas Jefferson University Hospital with the use of a Medical Graphics System 2001 CAD/Net™ (Medical Graphic Corporation, 350 Oak Grove Parkway, St. Paul, MN 55110). After the patient became familiar with the respiratory equipment, baseline isocapnic hypoxic ventilatory responsiveness was assessed by having the patient rebreathe from a 6-liter bag containing a gas mixture of 24% O_2, 7% CO_2, and balance nitrogen (Fig. 1). Oxygen concentration in the circuit decreased as it was consumed by the patient but normocarbia (±1 torr) was maintained with use of a variable CO_2 absorber bypass system. The resistance of the breathing circuit was 0.4 cm H_2O at a flow rate of 1 $L \cdot sec^{-1}$. Arterial oxygen saturation was measured with the use of an ear pulse oximeter. Minute ventilation was determined on an eight-breath averaging basis at arterial oxygen saturations from 100% through 70% (Fig. 2A). Forty to 70 points were used to construct each hypoxic response curve according to the method of least square regression analysis. Hypoxic ventilatory responsiveness was quantified by dividing the change in minute ventilation ($\Delta\ \dot{V}_E$) by the change in arterial O_2 saturation ($\Delta\ L \cdot min^{-1} \cdot \%O_2sat^{-1}$). This slope was calculated over the linear portion of the ventilatory response range (70–95% O_2 sat).

During the diagnostic procedure, all patients were monitored with an automatic blood pressure cuff, electrocardiograph and a pulse oximeter (Fig. 1). Patients were sedated with diazepam (Valium®), 2.5–5 mg iv by repeated bolus injections to maintain a

Table 1. Demographic Data and Slopes of the Ventilatory Response Curves to Hypoxia in 10 Patients After Sedation With Diazepam and After Flumazenil Administration

Case no.	Age (yr)	Weight (kg)	Duration of Sedation (min)	Dose (mg)	Slope ($L \cdot min^{-1} \cdot \%O_2\ sat^{-1}$)		
					Baseline	After Diazepam	After Flumazenil
1	39	77	55	55	3.1	2.5	1.9
2	32	52	85	80	1.1	0.4	0.6
3	42	60	85	115	1.5	0.7	1.0
4	36	54	135	210	2.9	2.7	2.5
5	44	95	115	110	3.3	3.2	3.0
6	38	64	210	72	1.0	0.9	1.5
7	36	82	90	95	2.3	1.8	3.0*
8	40	50	73	65	3.4	1.0	1.5
9	39	50	140	90	1.3	1.4	1.4
10	26	84	125	120	1.8	2.0	1.2

*This patient became very anxious after reversal with flumazenil.

Table 2. Degree of Sedation Before and After Diazepam and Flumazenil Administration

	Sedation Analog Score			Sedation Scale		
	Baseline	After Diazepam	After Flumazenil	Baseline	After Diazepam	After Flumazenil
Short	14 ± 23	96 ± 8*	40 ± 23†	1.0	3.4*	1.0†
Long	16 ± 32	90 ± 22*	26 ± 35†	1.0	3.6*	1.0†
Overall	15 ± 26	93 ± 16*	33 ± 29†	1.0	3.5*	1.0†

*Significantly different from baseline scores, $P < 0.05$.
†Significantly different from post-diazepam scores, $P < 0.05$.

stable level of sedation, such that they were resting comfortably but responsive to verbal stimulation. Immediately after completion of the procedure, the preoperative testing procedures were repeated as described before. Flumazenil 1.0 mg iv was then administered over 3–5 minutes. After reassessing their level of sedation with use of the analog scale and alertness rating, the hypoxic ventilatory responsiveness testing was repeated (5–10 minutes after flumazenil administration) in an identical fashion. Preliminary studies conducted at similar time intervals in eight young healthy volunteers revealed an average variability of 9–18% in the slopes of their hypoxic response curves over time (mean values ± SD were baseline 1.54 ± 0.59 [$r^2 = 0.96$], 60–180 minutes 1.49 ± 0.79 [$r^2 = 0.95$], and 70–190 minute 1.56 ± 0.70 [$r^2 = 0.98$]). The variance component estimate for the volunteers was 0.46 (with an error variance of 0.02).

Data are reported as mean values ± SD. Changes in ventilatory responsiveness were analyzed with the use of repeated measures of analysis of variance, with $P < 0.05$ considered statistically significant. Further data analysis was performed after subdividing the patients into two groups depending on the duration of sedation ($N = 5$ per group). The two groups ("short" ≤90 minutes and "long" ≥115 minutes) were compared using an unpaired *t*-test and two-way analysis of variance, with $P < 0.05$ considered statistically significant.

Results

Demographic data, baseline sedation values, and hypoxic responses are summarized in Table 1. Despite receiving an average diazepam dose of 0.97 ± 0.34 mg/minute (a total dose of 1.6 ± 0.8 mg/kg), only 5 of the 10 patients studied developed depressed hypoxic responsiveness after diazepam sedation. As expected, flumazenil significantly decreased diazepam-induced sedation (Table 2). Of the five patients with diazepam-induced depression of respiratory drive, only one had complete reversal of ventilatory depression after flumazenil administration (Table 1). In patient no. 1, the ventilatory response ($\Delta \dot{V}/\Delta O_2$ sat.) was even further depressed after flumazenil reversal (Fig. 2A–C).

When patients with evidence of depression of ventilatory drive after diazepam administration were compared with those patients with unchanged hypoxic responses (Tables 1 and 3), the only significant difference related to the duration of sedation (78 ± 14 *versus* 145 ± 37 minute). Although the diazepam dosages, sedation scores, and baseline ventilatory hypoxic responses were comparable for the "short"

Table 3. Effect of Duration of Sedation on the Slope of the Hypoxic Ventilatory Response

	Age (yr)	Weight (kg)	Sedation (min)	Diazepam Dosage (mg/min)	Hypoxic Response (L·min^{-1}·%O$_2$ sat^{-1})		
					Baseline	After Diazepam	After Flumazenil
Short	38 ± 4	64 ± 15	78 ± 14	1.0 ± 0.2	2.3 ± 0.9	1.3 ± 0.8*	1.6 ± 0.9
Long	37 ± 7	69 ± 19	145 ± 37†	0.9 ± 0.4	2.1 ± 1.0	2.0 ± 0.8†	1.9 ± 0.8
Overall	37 ± 5	67 ± 16	111 ± 44	0.97 ± 0.34	2.2 ± 0.9	1.7 ± 0.8*	1.8 ± 0.8

*Significantly different from baseline response, $P < 0.05$.
†Significantly different from short group, $P < 0.1$.

and "long" sedation groups (Tables 2 and 3), the hypoxic responsiveness at the end of the sedation period differed significantly (1.3 ± 0.8 *versus* 2.0 ± 0.8 L·min^{-1}·%sat^{-1}). In the absence of diazepam-induced respiratory depression, flumazenil had no effect on the slope of the hypoxic ventilatory response curve. However, flumazenil 1 mg iv was only partially effective in reversing the decreased slope of the hypoxic response curve after shorter periods of diazepam sedation (Table 3).

Discussion

Analogous to the findings of other investigative groups (4,12,13), we found significant variability in the respiratory response of subjects to diazepam (Table 1). Although most of our patients experienced varying degrees of ventilatory depression after diazepam, some subjects (no. 9 and no. 10) had slight increases in the slope of their ventilatory-response curves. Interestingly, Cohen et al. (2) reported less displacement of the CO$_2$-response curve when low-dose diazepam was administered in combination with meperidine than when the opioid analgesic was administered alone. These investigators suggested that diazepam might counteract the respiratory depressant effects of an opioid in some circumstances. A recent animal study (18) indicated that midazolam might also antagonize the analgesic properties of opioids. These data suggest that benzodiazepines can antagonize narcotic-induced respiratory depression.

Controversy surrounds the effectiveness of centrally-active antagonist drugs, physostigmine and naloxone, in reversing the sedative and respiratory depressant effects of diazepam. Anecdotal reports (19–21) suggest that physostigmine effectively reverses diazepam-induced sedation and respiratory depression. Using a double-blind protocol design, Garber et al. (22) were, however, unable to demonstrate any improvement in awareness or psychomotor function when physostigmine was administered to patients given sedative doses of diazepam. On the other hand, Bourke et al. (12) reported that physostigmine was effective in reversing respiratory depression caused by diazepam, whereas Spaulding et al. (23) reported increased awareness and a further decrease in ventilatory drive when physostigmine was administered to subjects sedated with diazepam.

Similar controversy exists regarding the respiratory effects of the benzodiazepine antagonist, flumazenil, when administered in the presence of diazepam-induced sedation and respiratory depression. Although flumazenil is recognized as effective in reversing benzodiazepine sedation and amnesia (24–27), data regarding its effects on resting ventilation and ventilatory drive are conflicting. Jensen et al. (25) found higher PaO$_2$ and lower PaCO$_2$ values in patients given flumazenil after general anesthesia with a benzodiazepine-nitrous oxide-narcotic-relaxant technique. Ricou et al. (27) reported that flumazenil was effective in reversing the decrease in vital capacity after sedation with midazolam. Forster et al. (28) reported that pretreatment with flumazenil could block midazolam-induced decreases in tidal volume, minute ventilation, and mean inspiratory flow. Flumazenil has also been found to reverse the depression of phrenic nerve activity after midazolam (29).

In fentanyl premedicated patients, the slope of the CO$_2$ response curve appeared to be decreased when flumazenil was administered to reverse midazolam-induced sedation (30). Thus, flumazenil may have the ability to "unmask" opioid-induced respiratory depression when administered in the presence of a benzodiazepine-opioid combination (Tolksdorf W, Bremer H, Tokic B, et al.). Respiratory depression after intravenous anesthesia (midazolam-fentanyl) not related to vigilance. 9th World Congress of Anesthesiologists Meeting, Washington, D.C., May 1988). Analogous to the observation of Spaulding et al. (23) after physostigmine-reversal of benzodiazepine sedation, evidence of persistent depression of ventilatory drive has been observed in some patients despite the fact that benzodiazepine-induced sedation was significantly decreased (30). These data suggest that the administered dose of flumazenil failed to reverse completely diazepam's effects at receptor sites within the central nervous system (CNS) that mediate depression of respiratory drive.

Although conflicting data exist in the anesthesia literature (7,31,32), high-dose naloxone has been reported to be effective in reversing diazepam-induced respiratory depression. Interestingly, in a recent study flumazenil was found to reverse midazolam-induced antagonism of morphine analgesia (18). These data suggest that the respiratory depressant effects of benzodiazepines may be related to nonspecific actions within the central nervous system. It is also possible that differing effects of benzodiazepines on the CNS medullary respiratory center (e.g., stimulation or depression) may be both dose and receptor (e.g., $GABA_B$ *versus* $GABA_A$) dependent. Further studies are needed to examine the CNS interactions between benzodiazepines, opioid analgesics, and the antagonist drugs.

We found that the effect of diazepam on the hypoxic ventilatory drive appeared to be related, at least in part, to the duration of sedation. In this preliminary study involving a small number of patients, ventilatory depression was not seen after a prolonged (>115 minutes) exposure to the benzodiazepine. Although "acute tolerance" to the CNS effects of diazepam has not been described in humans, Barnett and Fiore (33) reported diminished effects of repeated doses of diazepam on the depression of EEG activity in cats. Other investigators have described acute tolerance to the central respiratory effects of midazolam in the dog (34). Recently, Berggren et al. (35) evaluated the changes in respiratory pattern after repeated doses of diazepam and midazolam. Although both benzodiazepines produced decreases in tidal volume after the initial bolus dose, subsequent doses did not cause further changes in respiratory variables despite increased plasma drug concentrations. We speculate that prolonged exposure to a benzodiazepine may result in the development of tolerance to its respiratory depressant effects. Verification of the development of tolerance to the ventilatory effects of diazepam would require careful correlation between drug concentrations and respiratory drive over time.

In conclusion, we found that flumazenil produces variable effects on hypoxic ventilatory drive when administered after large doses of diazepam. In some patients with diazepam-induced ventilatory depression, the hypoxic response returned toward the presedation baseline value after flumazenil administration. In other patients, depression of respiratory drive persisted even though sedation was effectively reversed by flumazenil. These data indicate that the respiratory effects of diazepam may be related in part to non-benzodiazepine receptor mediated actions within the CNS. Our preliminary findings regarding the effects of diazepam and flumazenil on hypoxic ventilatory drive indicate the need for further studies to delineate the mechanism of this complex drug interaction.

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Electromechanical Effects of Protamine in Isolated Human Atrial and Canine Ventricular Tissues

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Effects of protamine sulfate (1–100 mg%) on the electrical and mechanical activities of isolated dog ventricular tissues and human atrial fibers were studied. In dog Purkinje fibers, 10 mg% protamine reduced markedly the maximum diastolic potential and the rate of phase 0 depolarization. Eventually, slow response action potential developed at a depolarized level and the twitch force declined abruptly. The depolarization and the negative inotropy were reversed by increasing [Ca])$_o$ or [K]$_o$ but not by tetrodotoxin. When Purkinje fibers were depolarized in 27 mM [K]$_o$ Tyrode solution plus 0.5 μM epinephrine, higher concentrations of protamine (30 mg% or above) were required to depress the slow response action potentials and twitch, in contrast to the action of verapamil and diltiazem (1–30 μM). Dog ventricular and human atrial muscle fibers were more resistant to the depressant effects of protamine. In human atrial fibers, however, 10 mg% protamine was able to depress significantly the oscillatory afterpotentials and aftercontractions induced by epinephrine and theophylline. The present findings suggest that the depolarization and decline in force of cardiac tissues induced by protamine, at a concentration about twice of the maximum clinically relevant dose, may be explained by the development of slow response action potentials as a result of decrease in membrane K$^+$ and Na$^+$ conductances.

Key Words: BLOOD, COAGULANTS—protamine. HEART, MYOCORDIAL FUNCTION—protamine.

Protamine sulfate is a strong polycationic polypeptide used extensively for heparin reversal after cardiopulmonary bypass (1). Adverse reactions to protamine, including hypotension and arrhythmias, have been reported (2,3). Release of histamine and the subsequent systemic vasodilation are important contributing factors (4), but less is known about possible direct cardiac effects. In isolated dog ventricular muscle, 5 mg% (50 mg/liter) protamine induced only a weak negative inotropic effect (−12%) that could be easily counteracted by the administration of $CaCl_2$ or epinephrine (5). In isolated right atrial and ventricular tissues from rabbit heart, the concentrations of protamine for 50% inhibition of isometric force (IC_{50}) were around 55 and 300 mg%, respectively (6). Reasons for the narrow margin between a dose producing modest depression and a dose leading to profound depression are unknown (6).

The purpose of the present study was to define the direct effects of protamine on action potential characteristics and contractile function of isolated dog ventricular tissues. The electropharmacologic effects of protamine were also studied on isolated human atrial tissue obtained at open heart surgery and compared with the effects of calcium channel blockers, verapamil, and diltiazem. Results of present study provide an electropharmacologic basis for the precipitous nature of hypotensive episodes during clinical protamine administration (7).

Methods

Mongrel dogs of either sex weighing 5–10 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.p.) and the heart was quickly excised. Strands of ventricular muscle and Purkinje fibers with a diameter of 1 mm or less were removed from ventricules. Atrial tissues obtained from hearts of 17 patients undergoing corrective cardiac surgery were also used. Institutional rules for the protection of human subjects were observed. Prior to surgery, informed consent was acquired. The tissue was immersed in cold Tyrode solution immediately after excision from the tip of the right atrial appendage as part of the routine atriotomy procedure. Strands of atrial trabe-

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cular muscle fibers with a diameter around 1 mm and a length of 3–6 mm were removed.

The preparations were placed in a tissue bath perfused with oxygenated (97% O_2 and 3% CO_2) Tyrode solution at 37°C. The composition of normal Tyrode solution was as follows (mM): NaCl 137, KCl 4, $NaHCO_3$ 11.9, NaH_2PO_4 0.5, $MgCl_2$ 0.5, $CaCl_2$ 2.7, and dextrose 5.5. In the high $[K]_o$ solution, $[K]_o$ was increased to 27 mM and 0.55 μM epinephrine was added. The preparations were driven at 60/min with suprathreshold electrical stimuli of 2 ms duration provided by a Grass S88 stimulator. One end of the preparation was fixed and the other end was connected to a Grass FT03C force-displacement transducer. Transmembrane potentials were recorded by means of glass microelectrodes filled with 3M KCl and connected to a Dagan 8500 preamplifier. Both electrical and mechanical events were displayed simultaneously on a Tektronix 5223 storage oscilloscope and a Gould ES1000 recorder or a Grass 7D polygraph. Occasionally, oscilloscopic tracings were recorded on Polaroid film with a Tektronix C-5C camera when needed.

Preparations were stabilized in normal Tyrode solution for 1 hour before experiements. Measurements were made of action potential amplitude, action potential duration at 50% repolarization (APD_{50}), maximum upstroke velocity of phase 0 depolarization ($\dot{V}_{max}$), maximum diastolic potential, and twitch force. Delayed afterdepolarizations (oscillatory afterpotentials) and triggered action potentials (8) were induced by epinephrine (0.1–1 μM) and theophylline (1–3 mM). Verapamil was obtained from Knoll Pharmaceuticals (F.G.R.), diltiazem from Tanabe Seiyaku (Taiwan, R.O.C.), protamine sulfate, and other chemicals from Sigma Chemicals (U.S.A.).

Values are expressed as mean ± SE. Statistical analysis was performed with use of the Student's t test; P values less than 0.05 were regarded as being statistically significant.

Results

Effects on fast response action potential

Figure 1A shows the effects of protamine (1–10 mg%) on the fast response action potential and contraction of a Purkinje fiber preparation driven in normal Tyrode solution. Protamine (3 mg%) changed very little the action potential characteristics and decreased slightly (−15%) the twitch force. At a higher concentration (10 mg%), however, protamine significantly reduced the maximum diastolic potential and $\dot{V}_{max}$ of phase 0 depolarization. Eventually, slow response action potentials developed at a depolarized level and the fibers became inexcitable. After recovery in drug-free solution, the same preparation was exposed to 3–30 μM verapamil. The calcium channel blocker significantly depressed twitch force at a concentration of 3 μM but changed $\dot{V}_{max}$ very little, even at a concentration as high as 30 μM.

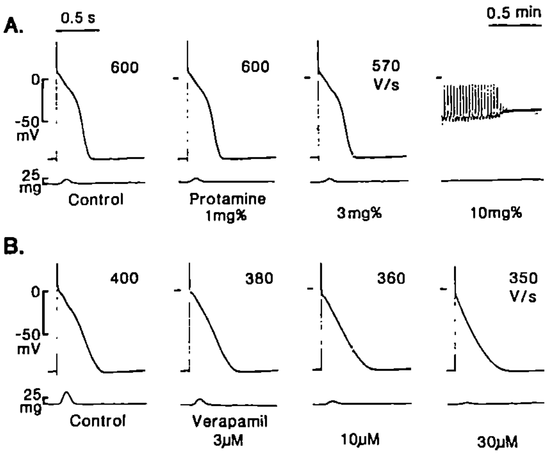

Figure 1. Effects of protamine (A) and verapamil (B) on the same Purkinje fiber preparation in normal Tyrode solution. In each panel, the action potentials (upper trace) and twitch curves (lower trace) were recorded before (control) and during cumulative doses of drug exposure. Time of each drug exposure was 5 min except in the last panel in A, which was recorded at a slower speed and the time of drug exposure was 11 min. Between A and B, the preparation was washed with drug-free Tyrode solution. The number in upper right corner of each panel indicates the value of maximal rate of phase 0 depolarization. In this and the following figures, the preparation was driven at 60 per min.

Table 1A summarizes the effects of 0.1–3 mg% protamine in nine preparations. In 12 of 18 preparations, Purkinje fibers became inexcitable at a potential level of −39.3 ± 3.4 mV after 12.7 ± 1.4 min exposure to 10 mg% protamine. In the remaining six preparations, slow responses developed with an average maximum diastolic potential of −33.2 ± 4.5 mV. Diltiazem (1–10 μM), a calcium channel blocker with higher specificity than that of verapamil (9), did not significantly affect $\dot{V}_{max}$ or amplitude of the action potential but dose-dependently reduced ADP_{50} and contractile force in six experiments (Table 2A).

The depolarization and the development of slow response action potential induced by 10 mg% protamine could be due to either a reduction of K conductance or an increase in cation fluxes. Figure 2 shows the progressive change in $\dot{V}_{max}$, the amplitude of phase 0 depolarization and the maximum diastolic potential induced by 10 mg% protamine. The reduction of diastolic potential appeared to be in parallel to that of $\dot{V}_{max}$. Also, administration of tetrodotoxin (0.3–1 μM) failed to prevent or reverse the reduction

Table 1. Effects of Protamine Sulfate on Action Potential Characteristics and Contractile Force of Dog Purkinje Fibers Bathed in 4 mM and 27 mM $[K]_o$ Solutions

	N	APA (mV)	$\dot{V}_{max}$(V/s)	APD_{50} (ms)	Force (%)
(A) 4 mM $[K]_o$					
Control	9	123.8 ± 3.7	323.3 ± 49.9	221.1 ± 23.1	100
Protamine					
0.1 mg%	9	124.7 ± 3.9	325.6 ± 52.1	236.7 ± 28.9	91.1 ± 4.3
1 mg%	9	122.9 ± 4.6	317.7 ± 52.7	224.4 ± 28.9	85.0 ± 4.1*
3 mg%	9	123.3 ± 3.2	307.6 ± 50.6	216.9 ± 21.9	82.4 ± 3.1*
(B) 27 mM $[K]_o$					
Control	10	52.6 ± 2.3	3.9 ± 1.3	88.6 ± 7.5	
Protamine					
1 mg%	4	53.0 ± 2.4	4.9 ± 2.6	98.0 ± 18.8	
10 mg%	9	50.0 ± 2.9	2.7 ± 1.1	91.7 ± 9.4	
30 mg%	7	42.1 ± 5.4	1.9 ± 0.5	102.7 ± 14.3	

*$P < 0.05$ (Student's *t* test) in comparison with control. APA = action potential amplitude; $\dot{V}_{max}$ = maximum upstrike velocity of depolarization; APD_{50} = action potential duration at 50% repolarization; N = number of preparations.

Table 2. Effects of Diltiazem on Action Potential Characteristics and Contractile Force of Dog Purkinje Fibers Bathed in 4 mM and 27 mM $[K]_0$ Solutions

	N	APA (mV)	$\dot{V}_{max}$(V/s)	APD_{50} (ms)	Force (%)
(A) 4 mM $[K]_o$					
Control	6	124.5 ± 4.8	395.0 ± 29.9	246.7 ± 40.1	100
Diltiazem					
1μM	5	129.4 ± 2.4	382.0 ± 15.6	264.0 ± 29.1	64.0 ± 3.6*
3μM	5	125.0 ± 2.7	388.0 ± 24.0	210.0 ± 22.6	38.8 ± 4.0*
10μM	6	119.7 ± 5.3	278.3 ± 54.3	153.3 ± 29.2*	21.7 ± 0.9*
(B) 27 mM $[K]_o$					
Control	4	46.5 ± 2.2	1.7 ± 0.4	70.0 ± 9.1	
Diltiazem					
1μM	3	27.3 ± 5.9*	1.1 ± 0.7	48.7 ± 4.7	
10μM	2	19.5 ± 2.5*	0.9 ± 0.6	40.0 ± 9.9	

* $P<0.05$ (Student's *t* test) in comparison with control. Abbreviations as in Table 1.

of diastolic potential in six experiments (not illustrated).

Antagonistic effects of high $[Ca]_o$ and high $[K]_o$

It has been reported that increasing $[Ca]_o$ can reverse the negative inotropic effect of protamine (5 mg%) in isolated dog ventricular muscle (5). In the present study, effects of high $[Ca]_o$ on the depressant effects of protamine were also tested in dog Purkinje fibers. As shown in Figure 3A, 10 mg% protamine induced typical electromechanical responses in a Purkinje fiber preparation. When the preparation became inexcitable at a potential level of −39 mV, increasing $[Ca]_o$ from 2.7–5.4 mM gradually shifted the potential level to more negative values and the fiber again responded to electrical stimuli. After exposure to high $[Ca]_o$ in the presence of protamine for 5 minutes, $\dot{V}_{max}$ returned to 55% of control value and twitch force increased to a level 72% above control value. Increasing $[K]_o$ from 4–6 mM also shifted the potential level to a more negative value (from −38– −52 mV) and partially restored excitability in protamine-depolarized fiber, but the $\dot{V}_{max}$ and twitch force remained significantly depressed (Figure 3B).

In five experiments, high $[Ca]_o$ (5.4–8.1 mM) consistently reversed the depressant effects of protamine, whereas 6 mM $[K]_o$ was effective only in three preparations.

Effects on high $[K]_o$ depolarized Purkinje fibers

Because high $[Ca]_o$ antagonized the depressant effects of protamine, it was important to see whether protamine depresses the calcium dependent action potential in preparations depolarized in 27 mM $[K]_o$ Tyrode solution in the presence of epinephrine. Under these conditions, Purkinje fibers were depolar-

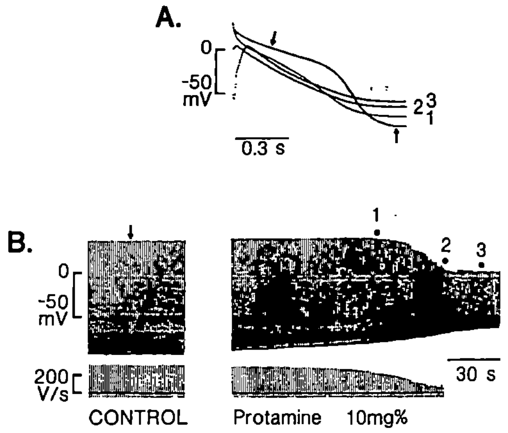

Figure 2. Progressive reduction of diastolic potential, maximal rate of phase 0 depolarization, and overshoot of action potential induced by 10% protamine. B panels show the slow-speed recordings of action potentials (upper traces) and their first derivatives (lower traces) before (CONTROL) and during 7–9th min of protamine exposure. Arrow (CONTROL) and dots 1 to 3 (Protamine) above the slow-speed traces indicate the time at which the superimposed action potentials showing in panel A were recorded.

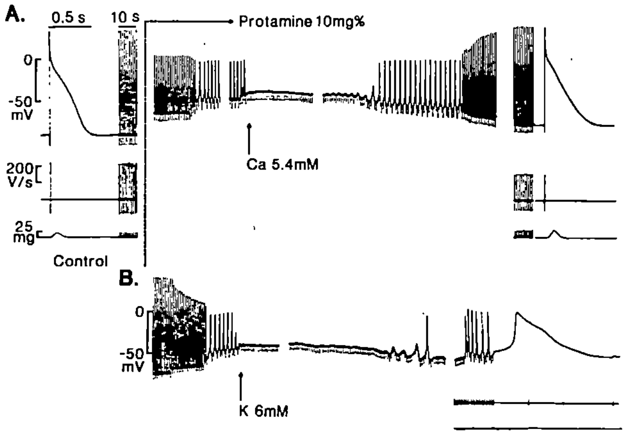

Figure 3. Antagonistic effects of high $[Ca]_o$ and $[K]_o$ on depolarization induced by protamine. In A, left panels show the control action potentials (upper trace), their first derivatives (middle trace), and twitch curves (lower trace) in fast and slow speeds. Middle panels show the progressive depolarization and inexcitability during 11th min of exposure to 10 mg% protamine. At the arrow, $[Ca]_o$ was increased from 2.7–5.4 mM. Right panel shows recovery of electromechanical activity after exposing the preparation to high $[Ca]_o$ plus protamine for 5 min. The preparation was then washed with normal Tyrode solution and exposed to protamine again. B panels began with recordings after 9 min of protamine exposure. $[K]_o$ was increased to 6 from 4 mM at arrow. Right panel was recorded during 9th min of exposure to high $[K]_o$ plus protamine.

ized to a potential level close to −40 mV and the slow response action potentials were generated mainly by transmembrance calcium influx (10). As shown in Figure 4A, exposure to 10 mg% protamine for 10 minutes reduced only slightly the amplitude and the upstroke velocity of slow response action potential in high K. Results of 10 experiments in high K-depolarized fibers are summarized in Table 1B.

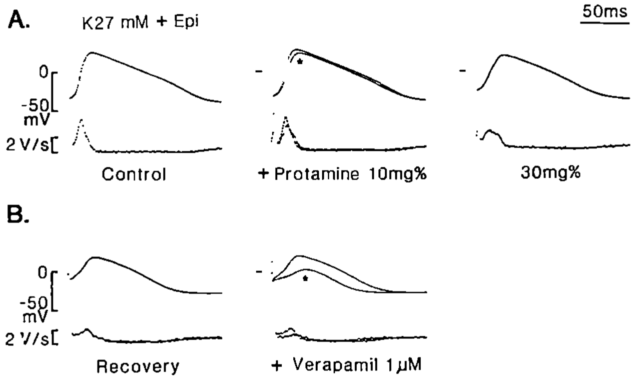

Figure 4. Depressant effects of protamine (A) and verapamil (B) on high-K depolarized slow response. In A, the left panel shows the control action potential (upper trace) and its first derivative (lower trace) in 27 mM $[K]_o$ Tyrode solution plus 0.5 μM epinephrine. In the middle panel, control traces are superimposed with those recorded during 5th min of exposure to 10 mg% protamine (asterisk). The right panel was recorded 5 min after the concentration of protamine had been increased to 30 mg%. In B, the left panel shows recovery after the Purkinje fiber was washed with control solution for 60 min. In middle B panel, recovery traces were superimposed with traces recorded during 5th min of exposure to 1 μM verapamil (asterisk).

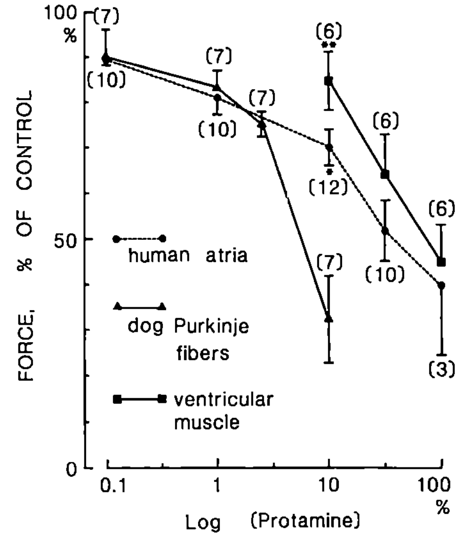

Figure 5. Dose-dependent negative inotropic effect of protamine on human atrial fibers (circles), dog Purkinje fibers (triangles), and dog ventricular muscle fibers (blocks). The abscissa indicates logarithmic concentrations of protamine. The ordinate is the percentage changes in contractile force as compared with the control values before protamine exposure. The number of preparations studied is given in parentheses. The vertical bar represents SE. In comparison with values of dog Purkinje fibers, $^{*}P < 0.05$, $^{**}P < 0.01$.

In contrast to the effect of protamine, the calcium channel blocker verapamil (1 μM) significantly depressed the upstroke velocity and the amplitude of the slow response action potential in the presence of high $[K]_o$ as shown in Figure 4B. In four of six preparations that had been exposed to diltiazem in

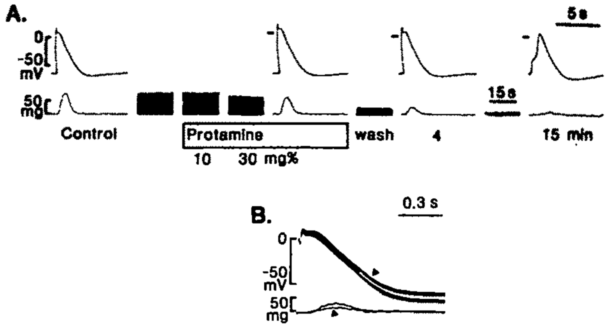

Figure 6. Depressant effects of protamine on human atrial tissue. The atrial preparation was treated with cumulative doses (0.1, 1, 10, and 30 mg%) of protamine. Time of drug exposure was 10 min for each concentration. In A, chart recordings of action potential (upper trace) and force (lower trace) were recorded before (control), during 10 and 30 mg% of protamine exposure, and during 4th and 15th min of washout (Wash). Time of drug exposure was 10 min for each concentration. In B, the oscilloscopic traces of action potential and twitch during 30 mg% protamine exposure and those during 4th min washout (arrow-heads) were superimposed.

normal $[K]_o$ Tyrode solution (Table 2A), the effects of diltiazem (1–10 μM) were tested again in 27 mM $[K]_o$ Tyrode solution (Table 2B). Similar to verapamil, diltiazem at a concentration of 1 μM also significantly depressed the slow response action potential developed in high K and more so at a higher concentration (10 μM).

Comparative inotropic effect in dog ventricular muscle fibers

In six experiments, the inotropic effect of protamine was also tested on ventricular trabecular muscle and compared with that on Purkinje fibers. Muscle fibers were consistently more resistant to the negative inotropic effects of protamine. The IC_{50} for protamine was 74 mg% in ventricular muscle and 6 mg% in Purkinje fibers (Figure 5). After washout, the recovery of force was almost complete (94.3 ± 10.1% of control) within 10 minutes.

Effects on human atrial fibers

Effects of protamine were also determined on atrial fibers obtained from 17 patients. The atrial preparations were treated with cumulative doses (0.1, 1, 10, 30 and occasionally 100 mg%) of protamine. As shown in Figure 6, protamine at concentration up to 10 mg% changed very little the force of contraction. At a concentration of 30 mg%, the force was decreased to 76% of control value, but the action potential characteristics was barely affected. During washout, however, the force decreased further and the diastolic potential shifted to a less negative value. Eventually slow response action potentials were induced and force declined abruptly (14% of control value). In eight preparations, the force during 30 mg% protamine exposure was 49.6 ± 7.4% of control value before drug exposure. After 10-minute washout, the force declined further to 30.6 ± 8.0% of control value. The difference (−18.9 ± 6.0%) was statistically significant ($P < 0.02$).

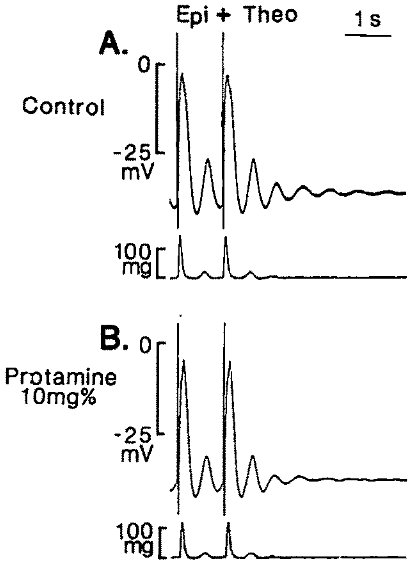

Figure 7. Depressant effect of protamine (10 mg) on triggered activity in a human atrial preparation. In both control (A) and test (B) panels, action potentials and twitch curves are shown in upper and lower tracings, respectively. After the last two driven beats, the electrical stimulation was terminated briefly to reveal the presence of delayed afterdepolarizations and aftercontractions. In B, time of protamine exposure was 10 min.

The IC_{50} for protamine in human atrial fibers was 24 mg%, which was between value for dog Purkinje fibers and that for dog ventricular muscle fibers. The IC_{50} was about the same in the presence of 1 μM epinephrine, but it was significantly increased when $[Ca]_o$ was elevated from 2.7 to 5.4 mM. High $[Ca]_o$ also reversed the negative inotropic effect of protamine in human atrial fibers as it did in dog Purkinje fibers. In three experiments, the twitch force was 39.0 ± 4.7% of control during protamine (30–100 mg%) exposure. When $[Ca]_o$ was increased from 2.7 to 5.4 mM, the twitch force became 114.7 ± 33.0% of the control value in normal Tyrode solution.

Human atrial tissue with slow response action potential is prone to develop triggered activity when the fiber is loaded with excessive amount of calcium or with cardiotonic drugs such as epinephrine and theophylline (11,12). As shown in Figure 7, an atrial preparation developed oscillatory afterpotentials and aftercontractions in the presence of 1 μM epinephrine and 1 mM theophylline. Protamine at a concentration of 10 mg% reduced the amplitude of the oscillatory afterpotential from 15–10.5 mV (−30%). The amplitudes of twitch and aftercontraction were reduced by about 20% and 30%, respectively. In another experiment, the amplitude of oscillatory afterpotential induced by 1 μM epinephrine was 9 mV. The value was reduced to 3 mV in the presence of 30 mg% protamine.

Discussion

The present study shows that in isolated dog ventricular and in human atrial tissues protamine (3–100 mg%) induces a dose-dependent negative inotropic effect. Dog Purkinje fibers were particularly sensitive to the depressant effect of protamine in that, at a concentration of 10 mg%, protamine progressively reduced the diastolic potential and the upstroke velocity and amplitude of phase 0 depolarization. Eventually, the fibers became inexcitable at a depolarized level. This concentration of protamine is about twice of the maximum dose used clinically (4 mg/kg of body weight), assuming that the injected protamine distributes evenly into the circulating blood volume of 75 ml/kg of body weight (5,6). Considering the individual variation in drug sensitivity, the possible deleterious effect on ventricular conducting tissue could lead to the hypotension that may be observed during *in vivo* protamine administration in humans (7).

Unlike calcium channel blockers (verapamil and diltiazem), protamine induced less depressant effect on high-K depolarized slow response than that on normal K fast response action potential, suggesting a smaller inhibitory effect on calcium channel than on sodium channel. The depolarization induced by protamine may be due to a decreased K conductance because it is in part reversed by increasing $[K]_o$ from 4–6 mM. Similar reversal effect of increased $[K]_o$ on membrane depolarization have been observed in digitalis-intoxicated Purkinje fibers (13). One possibility among others for this effect is that protamine as a polycation can have surface charge effects at the membrane that may alter the conformation of ion channels (14). Increased $[Ca]_o$ may reverse depolarization and inexcitability by displacing protamine from its binding site at the sarcolemma and thus restor excitability. High $[Ca]_o$ may also reverse the depressant effect of protamine through an increased calcium influx and the subsequent activation of a Ca-dependent K channel (15). Therefore, the abrupt depolarization and decline in force induced by protamine could be explained by the development of slow response action potentials as a result of a reduction in K and Na conductance.

The negative inotropic effect of 10 mg% protamine sulfate on dog ventricular muscle fibers was rather weak (−15.8 ± 7.2%, Fig. 5). This magnitude of depression in force is close to that induced by 5 mg% protamine in dog ventricular trabeculae as reported by Iwatsuki et al. (5). The IC_{50} for protamine in human atrial fibers (24 mg%) is similar to that observed in rabbit left atria (around 20 mg%) but lower than that in rabbit right atria (around 55 mg%). The reason for the different sensitivity to rabbit left versus right atria is not known (6). Nevertheless, the greater negative inotropy and the lesser recovery after washout of protamine in human atrial fibers (Fig. 6) than in dog ventricular muscle in the present study are in agreement with the findings that protamine induces a greater depressant effect on atrial tissue (6). Another important finding in human atrial fibers is that, in addition to the negative inotropy, 10–30 mg% protamine was able to decrease the amplitude of the oscillatory afterpotentials and aftercontractions induced by cardiotonic drugs. Therefore, similar to calcium channel blockers (11,12), inhalational anesthetics (16), and somatostatin (17), protamine may depress the triggered activity (8) in human atrial fibers through a reduction of the cellular calcium or the oscillatory inward currents during diastole.

It has been demonstrated in human subjects that the administration of protamine increases plasma histamine levels (4). The mammalian heart has histamine receptors and contains large amounts of histamine. Both histamine release and intracardiac administration of histamine are associated with increases in heart rate and contractility and the induction of arrhythmias (18). Results of electrophysiologic studies on both human (19) and nonhuman mammalian cardiac tissues (20) reveal that histamine increases the firing rate, the phase 0 $\dot{V}_{max}$ and the maximum diastolic potential. These effects are in contrast to those induced by protamine in human atrial and dog ventricular tissues in our study. Therefore, histamine released from cardiac tissues, if any, could not account for the observed depolarization and decline in force during protamine exposure in the present experiments. However, it remains to the clarified whether or not the deleterious effect after washout of protamine observed in human atria is related to the removal of the potentiation induced by the local release of histamine. Further investigations are required to explore the interaction between histamine and protamine in the heart.

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Pseudocholinesterase Activity in Human Cerebrospinal Fluid

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KAMBAM JR, HORTON B, PARRIS WCV, HYMAN SA, BERMAN ML, SASTRY BVR. Pseudocholinesterase activity in human cerebrospinal fluid. Anesth Analg 1989;68:486–8.

Pseudocholinesterase (PCHE) activity and dibucaine numbers (DN) in the cerebrospinal fluid (CSF) and plasma of 10 ASA physical status 1 and 2 patients were measured using a kinetic method. CSF had a mean PCHE activity of 0.018 ± 0.013 unit/ml with a DN of 59 ± 4. Whereas, PCHE activity and DN in the plasma were 0.960 ± 0.12 units/ml and 84 ± 3, respectively.

We also measured PCHE activity and DN in the CSF and plasma of 4 patients in whom there was a recent history of intraventricular bleeding. These patients had a CSF PCHE activity of 0.340 ± 0.07 units/ml (DN = 78 ± 3) and a plasma PCHE activity of 0.950 ± 0.10 units/ml (DN = 82 ± 2).

Our data show that there is a low activity of PCHE in CSF, 1/20–1/100th that of plasma. Our data also show that PCHE activity increased to 1/4 to 1/2 that of plasma in CSF of patients with bleeding into CSF.

Key Words: Ezymes: pseudocholinesterase SPINAL CORD—Cerebrospinal fluid.

Vascular absorption of local anesthetics is believed to be the primary reason for the decrease in concentration of local anesthetic drug in cerebrospinal fluid (CSF) and for the termination of spinal anesthesia (1). Investigators provide conflicting data regarding the metabolism of ester type local anesthetics in the CSF (2,3). Pseudocholinesterase (PCHE) is primarily responsible for the metabolism of ester type local anesthetics including procaine, 2-chloroprocaine, cocaine, and tetracaine. There is a paucity of information concerning PCHE activity in human CSF. Available data regarding the amount of CSF PCHE activity have been conflicting (4). Moreover, the dibucaine number (DN) of the CSF PCHE have not been reported. This is important because determination of DN differentiates normal from atypical pseudocholinesterase and that atypical PCHE hydrolyzes local anesthetics at a much lower rate when compared to normal enzyme.

Spinal taps associated with bleeding into CSF may produce significant elevation of PCHE activity in the CSF depending on the severity of bleeding. Since PCHE is responsible for the metabolism of ester type local anesthetics, any bleeding into CSF may shorten the duration of spinal anesthesia produced by ester type of local anesthetics.

The purpose of our present study was to determine PCHE activity and DN in the CSF and plasma of patients with clear and with blood tinged CSF.

Methods

With prior approval of our Institutional Review Board for the Protection of Human Subjects, we included 10 ASA physical status 1 and 2 patients (ages 22–70; *Group 1*) in this study. Informed consent was obtained from all patients, each scheduled for spinal anesthesia for either transurethral resection of prostate or bladder tumor, or repair of an inguinal hernia. Patients were receiving no medications preoperatively that affect PCHE activity. One ml of CSF was collected from all patients prior to injection of local anesthetic solution into CSF; 3 ml of heparinized venous blood were also collected from all the patients prior to induction of spinal anesthesia. Plasma was separated from the blood samples.

We also collected 3 ml of heparinized venous blood and 1 ml of CSF from one of the cerebral ventricles in 4 patients (ages 30–50 yrs; *Group 2*) in whom there was a recent (7–10 days prior to craniotomy) history

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Table 1. Pseudocholinesterase (PCHE) Activity (units) and Dibucaine (DN) of Cerebrospinal Fluid (CSF) and Plasma in 10 ASA Physical Status 1 and 2 Patients (Group 1).

Subjects	CSF		Plasma	
n=10	PCHE	DN	PCHE	DN
1	0.008	51	0.85	82
2	0.025	65	0.92	81
3	0.006	61	0.82	86
4	0.040	54	1.00	88
5	0.010	56	0.90	85
6	0.040	63	0.99	85
7	0.011	59	0.84	80
8	0.009	59	1.20	86
9	0.011	62	1.10	82
10	0.020	61	0.96	81
Mean	0.018	59	0.96	84
SD	0.013	04	0.12	03

of bleeding into CSF. Patients in Group 2 were receiving general endotracheal anesthesia (sufentanil, vecuronium and N_2O in O_2) when the samples were collected. PCHE activity and DN were also measured in both CSF and plasma of Group 2 patients.

PCHE activity and DN were measured in both CSF and plasma samples of all the patients using a kinetic method described by Zapf et al. (5). The kinetic method using naphthyl acetate substrate was used because of assay's specificity for PCHE activity and because the presence of acetylcholinesterase would not interfere with the measurements of PCHE. PCHE activity is expressed as units/ml plasma or CSF. One unit corresponds to the liberation of 1 mmole of 1-naphthol per minute under the conditions of the enzyme assay (5).

The linearity of both PCHE assay in the ranges reported for CSF and the naphthol standard curve was also studied as the lower limits of linearity of the assays were not studied by Zapf et al. (5). To evaluate the accuracy of DN at low PCHE levels, we also determined DN in the plasma samples with serial dilutions of up to 100-fold.

Results

Table 1 contains the individual and mean values of CSF and plasma PCHE activities and DN in patients from Group 1. The mean PCHE activity of CSF samples of Group 1 patients was 0.018 ± 0.013 units with a DN of 59 ± 4. The results in Table 1 show that the CSF PCHE activity is 1/20–1/100th that of plasma. Our results also show DN in CSF to be significantly lower than DN in plasma.

Table 2. Pseudocholinesterase (PCHE) Activity (unit) and Dibucaine (DN) of Cerebrospinal Fluid (CSF) and Plasma of 4 Patients (Group 2) with History of Recent Hemorrhage into CSF

Subjects	CSF		Plasma	
n=4	PCHE	DN	PCHE	DN
1	0.282	76	0.95	80
2	0.310	75	0.91	82
3	0.320	79	1.10	84
4	0.448	82	0.89	82
Mean	0.340	78	0.95	82
SD	0.070	03	0.10	02

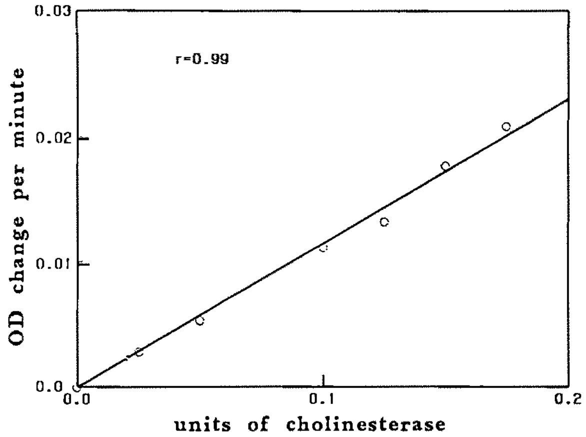

Figure 1.

The CSF and plasma PCHE activities and DN in Group 2 patients with intraventricular bleeding are shown in Table 2. The CSF PCHE activity in these patients was 1/4–1/2 that of plasma. There is no significant difference in the DN between plasma and the CSF in Group 2 patients, suggesting that the source for the elevated PCHE in the CSF was from the recent hemorrhage into CSF. No significant alterations in DN were found with serial dilutions of plasma. The undiluted plasma samples had DN values of 80–84, whereas diluted plasma samples had DN values of 80–88.

The linearity of PCHE assay is shown in Figure 1. Fresh human butyryl cholinesterase was used to run the control assay. The PCHE assay appears to be linear (r = 0.99) especially at the low OD changes where the CSF PCHE and DN assays were run. Figure 2 shows that the naphthol standard curve is linear even to the lowest readable value in our spectrophotometer (r = 0.99).

Discussion

Several investigators studied the content and characterization of cholinesterases in human CSF (1). Inves-

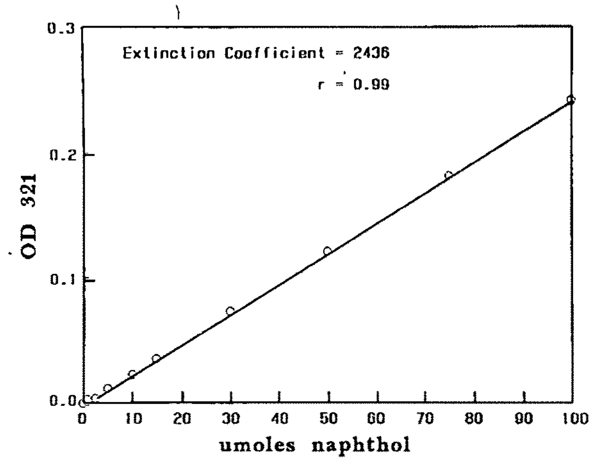

Figure 2.

tigators reported that acetylcholinesterase (true cholinesterase) is the chief cholinesterase present in the CSF. Data on CSF PCHE from previous investigators show wide variations in the enzyme activity (1/20–1/250th that of plasma). However, none of the previous reports studied the DN or an equivalent test characterizing the type of PCHE in CSF. Our present data on CSF PCHE agree with the previous reported results. Our results also show DN values to be lower in CSF than in plasma of the same patients. The reasons for lower DN in CSF are not clear. The different composition of CSF compared to plasma may be responsible for these lower CSF DN values. On the other hand, the CSF PCHE may be another isoenzyme of PCHE with a lower DN. To date at least twelve isoenzymes of PCHE have been identified in human plasma (6).

Helrich et al. (2) studied the fate of intrathecal procaine and concluded that the decline of procaine concentration in the CSF is not due to chemical breakdown of the drug. Schmidt studied the in vitro metabolism of procaine in CSF with the addition of traces of blood and reported that there was no significant metabolism of procaine (7). Schmidt and Helrich measured neither plasma nor CSF PCHE activity in the samples they used in their studies. Foldes et al. (3) reported that the hydrolysis of procaine and 2-chloroprocaine in spinal fluid is about 1/3rd faster than in buffer solutions of identical pH. Foldes et al. also showed that the hydrolysis of 2-chloroprocaine in spinal fluid is partly alkaline and partly enzymatic and the rate of hydrolysis is 25–100 times slower than in plasma. Foldes et al. also did not measure PCHE activity in the CSF samples they used in their study. Our present data indirectly agree with Foldes et al. as we have shown the CSF PCHE activity to be 1/20th to 1/100th that of plasma.

In conclusion, our results confirm that CSF has a low PCHE activity. The PCHE activity that is present in CSF is probably clinically insignificant for the metabolism of ester type of local anesthetics in CSF. It is also apparent from our study that the CSF PCHE had much lower DN when compared to plasma DN. Our data also suggest that in patients with blood-tinged CSF there is a significant PCHE activity in the CSF which may be clinically important when ester type local anesthetic is administered for spinal anesthesia and/or for the diagnosis of pain syndromes.

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Considerations for Anesthetic Management During Veno-venous Bypass in Adult Hepatic Transplantation

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PAULSEN AW, WHITTEN CW, RAMSAY MAE, KLINTMALM GB. Considerations for anesthetic management during veno-venous bypass in adult hepatic transplantation. Anesth Analg 1989;68:489–96.

Intraoperative data from 42 adult orthotopic hepatic transplant recipients were analyzed retrospectively to assess the hemodynamic, coagulation, and thermal effects of heparinless veno-venous bypass using a constrained vortex pump. Transient hemodynamic changes occurring at the onset of bypass included decreases in temperature (−10.7%), heart rate (−18.7%) and arterial pressure (−15.1%); and increases in central venous pressure (27.6%) and ECG T wave amplitude (231.6%). Abrupt decreases in cardiac output and pump flow occurred with termination of the portal limb of bypass, which is required to allow completion of the portal vein anastomosis. However, significant continuous decreases were observed in bypass flow and cardiac output during the entire bypass period. The blood volume became concentrated as indicated by increases in hematocrit, colloid osmotic pressure, serum osmolality and serum sodium. Changes in colloid osmotic pressure were inversely related to bypass flow. These data, along with an accumulating base deficit, suggest that veno-venous bypass is associated with less than optimal perfusion of the abdomen and lower extremities. Flow dependent third space fluid accumulation is most likely responsible for decreasing cardiac output and pump flow during the bypass period.

No clinically significant coagulopathy could be attributed to the use of veno-venous bypass. There were no significant changes in platelet counts, fibrinogen levels or prothrombin times. The activated partial thromboplastin time decreased from 60.5 to 50.2 seconds.

Patient core temperature decreased three times more rapidly (0.9°C/hr) during bypass than at any other time during the procedure.

Key Words: LIVER, transplantation. SURGERY, TRANSPLANTATION: Liver.

This study explores the hemodynamic, coagulation, and thermal effects of heparinless veno-venous bypass during adult orthotopic hepatic transplantation. The anhepatic phase of the surgical procedure is characterized by abdominal venous congestion, increased venous pressure and decreased venous return due to cross-clamping of the suprahepatic vena cava. The need for venous decompression to avoid the development of shock during experimental canine hepatic transplantation was demonstrated by Moore et al. (1) and Starzl et al. (2) in 1960. In order to improve hemodynamics, these investigators employed plastic catheters that drained blood from the inferior vena cava and the splanchnic circulation (sometimes via construction of a porta caval shunt), and returned the blood to the jugular vein. The first clinical hepatic transplantations (3) reported in 1963 also employed these techniques, but suffered from a high incidence of embolic phenomena. In 1979, Calne et al. (4) reported the use of partial cardiopulmonary bypass between the femoral vein and femoral artery of liver transplant patients in order to alleviate cardiovascular instability resulting from occlusion of the vena cava. While providing the desired cardiovascular stability, the heparinized pump-oxygenator circuit resulted in uncontrollable bleeding despite attempted protamine reversal.

Veno-venous bypass has been suggested (5) for venous decompression, improved hemodynamic stability and decreased intraoperative blood loss. In addition, veno-venous bypass has been reported to improve renal function, decrease mortality, and pro-

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vide additional time for completion of the vascular anastomoses. Figure 1 illustrates the routine connection of the extracorporeal bypass circuit to the abdominal vasculature as previously described by Denmark et al. (6) and Griffith et al. (7). Blood is pumped from the portal and femoral veins using an extracorporeal circuit containing a constrained vortex pump, without the use of heparin or heparin bonded tubing, and returned to the axillary vein.

The routine use of veno-venous bypass during the anhepatic phase of adult hepatic transplantation remains controversial. Some transplant centers employ veno-venous bypass routinely (5,8); others use various bypass techniques only for specific diagnoses or when suprahepatic vena cava occlusion is not tolerated (9,10); and few centers do not use bypass (11). The question of whether or not to use bypass is not easily answered. However, some insight into the cardiovascular consequences of not using bypass may be gained from extrapolation of the data presented here as the bypass pump flow decreases toward zero.

Hypothermia during transplantation may pose another significant problem, as demonstrated by Aldrete et al. (12). Hypothermia may be potentiated during the anhepatic phase of the procedure by the use of an extracorporeal circuit that does not contain a heat exchanger. Heparinless veno-venous bypass cannot use a classic heat exchanger because of the large potentially thrombogenic surface area that could lead to fibrin deposition and the release of emboli into the patient. The theoretical heat loss from the bypass circuit is investigated to estimate the contribution of the extracorporeal bypass circuit to the total heat loss from the patient during the anhepatic phase.

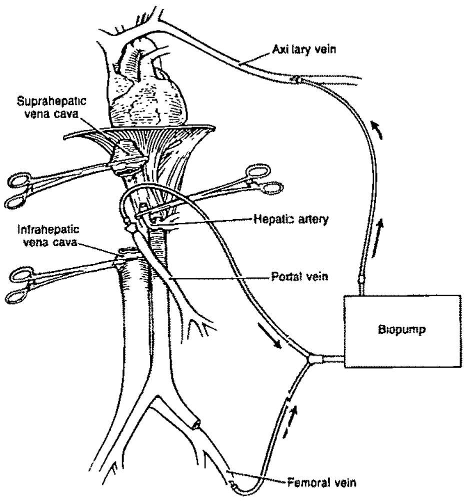

Figure 1. Diagram depicting the routine implementation of veno-venous bypass in the adult patient.

Materials and Methods

Data from 42 consecutive adult patients undergoing hepatic transplantation for end stage liver disease were reviewed retrospectively. All patients were positioned on a heating blanket set to 38°C and were ventilated through a Fisher Paykel dual servo heated humidifier. Routine hemodynamic and metabolic monitoring included: radial or brachial artery pressure measurements; pulmonary artery and central venous pressures and cardiac output measurements from a thermal dilution Swan Ganz catheter; heart rate; simultaneous measurement of ECG leads II and V5; esophageal, rectal and pulmonary artery temperatures; mass spectrometer for analysis of inspired and exhaled gases; arterial blood gas tensions; Na^+, K^+, Ca^{++}, blood glucose levels, serum and urine osmolarity; and arterial colloid osmotic pressure. Systemic and pulmonary vascular resistances were computed in the standard manner. Coagulation was monitored by thrombelastography and coagulation profiles.

The bypass circuit consisted of a Biomedicus model 520 console and a model 600 Bio Pump (154 ml volume) with 0.95 cm internal diameter tubing. The inlet tubing to the Bio Pump was a 2.1-meter length of Gish Mediflex 0.95 cm × 0.24 cm tubing. The patient return was composed of an 20.3 cm length of the Gish tubing, the Biomedicus Bio-Probe Insert (model DP38), and a 1.5 meter length of Tygon 0.95 × 0.24 cm tubing. The bypass circuit was primed with 440 ml of room temperature Plasmalyte A. Blood flow in the bypass circuit was measured using the integral electromagnetic flowmeter of the Biomedicus model 520 console.

Hepatic artery and portal vein ligation marked the beginning of the anhepatic phase of the surgical procedure. Gott shunts were placed into the femoral and portal veins, connected together (Fig. 1) with a Y adapter and to the pump inflow tubing. The blood was returned by the pump into the axillary vein. Bypass was initiated immediately before clamping the suprahepatic cava. Bio Pump flow was determined by increasing the speed until no further increase in flow could be obtained. Complete sets of measurements related to this study were acceptable only when they were obtained no more than 20 minutes before the start of the anhepatic phase, approximately 15 minutes following the onset of bypass to allow the settling of hemodynamic transients, within 15 minutes prior to termination of portal bypass, and 10 minutes prior to revascularization of the donor organ. In addition, a series of cardiac outputs and resistances were obtained along with pump flow rates every 10 minutes during the bypass period. Statistical significance was assumed when $P \leq 0.05$ as computed using the paired Student's *t* test.

Pulmonary artery temperature; heart rate; ECG lead V5; and central venous, pulmonary artery and systemic arterial pressures were recorded continuously during the bypass period. A best subset regression analysis was performed on the data from each patient, and on all patients grouped together, to uncover the factors that determine the Bio Pump flow. The factors evaluated included cardiac output, mean arterial pressure, central venous pressure, pulmonary artery mean and diastolic pressures, heart rate, systemic vascular resistance, and pulmonary vascular resistance.

Simple linear correlations were performed on all the laboratory data to uncover relationships between the changes in laboratory data, blood product use during bypass, and mean Bio Pump flows during bypass.

The potential contribution of the extracorporeal bypass circuit to the total heat loss was examined in a separate set of experiments. The standard pump circuit was connected to a constant temperature water bath set at 36.9°C (±0.2 SD), which simulated the patient component of the bypass loop. Thermistors were located at the inlet and outlet of the circuit to measure the temperature drop as the room temperature and pump flow were varied. Heat loss from the extracorporeal circuit was then computed as a function of room temperature and pump flow. Substituting the specific gravity (1.045 g/cm^3) and specific heat of blood (0.87 cal/g°C) for distilled water into the calculations of heat loss permitted the estimation of heat loss for blood circulating through the pump circuit (13).

Results

Data presented here were taken from a retrospective review of 42 consecutive adult transplant recipients and represent available data relatively free of technical difficulties and prophylactic pharmacologic therapy that may have biased the data. Of the 42 patients, 35 had veno-venous bypass as described above; five underwent only femoral vein bypass due to blood clots in the portal vein or technical difficulties during cannulation; bypass was terminated in one patient after a few minutes due to inadequate bypass flow (less than 1 L/M); and one patient died during the bypass procedure.

Table 1. Bio Pump Flow Rates Associated with the Phases of Veno-Venous Bypass. Data are expressed as the Mean ± 1 Standard Deviation

	Bypass (n = 35)	Portal (n = 32)	Unclamping (n = 32)
Bio Pump Flow (liters/minute)	2.5 ± 0.6	2.2 ± 0.5	1.7 ± 0.5
% Difference		−6.1 ± 23.0	−21.2 ± 20.8
Significance		$P < 0.025$	$P < 0.001$

For purposes of this presentation, veno-venous bypass has been divided into four phases: the initiation of bypass (BYPASS); the period immediately prior to the termination of portal bypass leaving only flow from the femoral vein into the bypass circuit (PORTAL); the time immediately before unclamping of the portal vein and inferior vena cava (UNCLAMPING); and termination of femoral bypass (TERMINATION). The mean duration of the portal phase was 54.1 min (±14.3 SD; n = 32). From the onset of bypass to the time of unclamping, averaged 68.7 min (±13.6 SD; n = 39). The mean total time from the initiation of bypass to the termination was 81.5 min (±18.5 SD; n = 39).

Mean Bio Pump flows for each of the phases of bypass, excluding the flow at termination for which the data was too sparse to present, is illustrated in Table 1. Bypass flow progressively decreased from each phase to the next. The percent differences were computed from paired data. The mean Bio Pump flow rates for five patients who received only femoral bypass was 1.7 (±0.7 SD) L/M at the start of bypass, with an apparent increase to 2.0 (±0.8 SD) L/M. The bypass flows following the onset of veno-venous bypass were significantly lower in the femoral bypass group than in the portal + femoral bypass patients. Prior to unclamping, bypass flows were similar in both groups.

Following the initiation of bypass, there were transient hemodynamic effects that rarely persisted for more then 30 seconds (Table 2). The changes in heart rate were linearly correlated with the changes in temperature. Decreased arterial pressure occurred with the changes in heart rate. Similar increases in central venous and pulmonary artery pressures were observed along with extremely large increases in T wave amplitude recorded from ECG lead V5.

To determine whether the decrease in arterial pressure was related to a transiently depressed myocardium, or the direct effects of the cold priming solution on the vasculature, the time between the peak effects of the heart rate change and the peak effects of the blood pressure change were measured. The time from the peak temperature change mea-

Table 2. Transient Hemodynamic Changes With the Onset of Veno-Venous Bypass. Data are expressed as the Mean ± 1 Standard Deviation

	Prebypass	Bypass	Percent change	n	Significance
Temperature (degrees C)	35.2 ± 0.8	31.4 ± 1.5	−10.7 ± 3.4	25	$P < .001$
Heart Rate (beats/min)	90.3 ± 14.9	73.8 ± 14.3	−18.7 ± 6.9	25	$P < .001$
Art. Press. (mm Hg)	79.2 ± 11.3	67.2 ± 11.7	−15.2 ± 8.5	25	$P < .001$
Pul. Art. Press. (mm Hg)	17.4 ± 4.9	19.9 ± 5.8	15.0 ± 13.3	25	NS
Cen. Ven. Press. (mm Hg)	9.8 ± 4.6	12.1 ± 5.2	27.6 ± 24.6	25	$P < .05$
T Wave Ampl (mm)	1.2 ± 0.7	3.9 ± 2.3	231.6 ± 122.2	22	$P < .001$

sured in the pulmonary artery to the peak change in heart rate was 8.9 sec (±4.4 SD; n = 24). The time from the peak temperature change to the peak change in arterial pressure was 12.6 sec (±8.8 SD; n = 22). The difference between the changes in heart rate and arterial pressure is approximately 4 seconds, probably too little time to account for a direct effect upon the circulation.

Changes in physiologic variables that occurred following the onset of bypass, after the transients had dissipated, are summarized in Table 3. The heart rate response was variable in each phase resulting in no significant differences. Following the onset of bypass the central venous pressure remained statistically unchanged while the pulmonary artery pressures decreased despite increased pulmonary vascular resistance. Cardiac output and stroke volume decreased, but the increase in systemic vascular resistance elevated arterial pressure. Until termination of portal bypass, the arterial pressure declined to almost pre-bypass levels, while cardiac output and stroke volume continued to decrease. Pulmonary vascular resistance continued to increase. Following termination of portal bypass, mean pulmonary artery pressure decreased along with continued decreases in cardiac output and stroke volume. Systemic vascular resistance increased resulting in maintenance of arterial pressure. With reference to Tables 1 and 3, cardiac output during bypass decreased by 2.8 L/M, of which 0.7 L/M (26.3%) could be attributed to decreased return from the bypass circuit.

Cardiovascular changes in the five patients who received only femoral bypass included significantly lower bypass flows upon initiation and significantly greater decreases in cardiac output during the bypass period. Otherwise, the progressive hemodynamic changes were similar with both types of bypass.

Coagulation profiles and laboratory data were used to construct Table 4. During bypass the activated partial thromboplastin time (APTT) demonstrated a statistically significant decrease without a significant change in prothrombin time (PT). Platelet counts and fibrinogen levels remained unchanged, as did potassium, ionized calcium and pH values. The oncotic pressure increased along with a slight increase in serum osmolality and serum sodium levels. The increase base deficit suggested an accumulating metabolic acidosis. Only one significant relationship emerged from the linear regression analysis as demonstrated in Figure 2. Oncotic pressure was inversely related to Bio Pump flow.

There were no simple linear relationships or simple linear combination of hemodynamic factors that could satisfactorily account for the Bio Pump flow. In an individual patient a single factor could be correlated with pump flow, but the factor was different for almost every patient. When the patients were grouped together the strongest contributor to the correlation was cardiac output, which had a poor correlation coefficient of 0.50.

Heat loss in patients during veno-venous bypass was evaluated by comparing the rate of temperature change during the preanhepatic phase with the rate of temperature change during bypass. Temperature decreased at a rate of 0.3°C/hour (±0.17 SD; n = 24) during the preanhepatic phase compared to 0.9°C/hour (±0.37 SD; n = 24) during bypass.

Figure 3, constructed from the bypass circuit heat loss experiments, illustrates the relationship of pump flow rate and room temperature to the temperature difference measured between the inlet and outlet of the bypass circuit. Figure 4 illustrates the heat loss in kilocalories per minute estimated from the temperature differences, and accounting for the differences

Table 3. Physiologic Variables Related to the Phases of Veno-Venous Bypass and the Changes in these Variables Between the Phases. Data are expressed as the Mean ± 1 Standard Deviation.

	Prebypass (n = 34)		Bypass (n = 34)		Portal (n = 26)		Unclamping (n = 26)
Heart Rate (Beats/Minute)	94.0 ± 13.5		93.7 ± 14.9		94.4 ± 15.2		91.9 ± 15.4
% Difference		0.1 ± 12.0		0.6 ± 10.3		−1.9 ± 5.9	
Significance		NS		NS		NS	
Art. Pressure (mm Hg)	72.6 ± 11.0		77.5 ± 13.1		71.7 ± 11.6		76.6 ± 15.2
% Difference		7.9 ± 16.6		−4.3 ± 13.6		6.7 ± 20.1	
Significance		$P < 0.005$		$P < 0.05$		NS	
Cent Ven Press (mm Hg)	11.3 ± 4.4		11.5 ± 4.0		11.7 ± 4.0		11.3 ± 4.6
% Difference		4.8 ± 18.8		−1.6 ± 16.6		7.8 ± 46.7	
Significance		NS		NS		NS	
Pulm Art Mean (mm Hg)	18.3 ± 6.2		15.9 ± 4.8		16.9 ± 5.2		15.8 ± 5.3
% Difference		−10.4 ± 20.4		1.7 ± 17.6		−4.6 ± 8.6	
Significance		$P < 0.001$		NS		$P < 0.025$	
Pulm Art Dias (mm Hg)	10.8 ± 3.9		9.0 ± 3.9		9.7 ± 3.6		9.4 ± 3.4
% Difference		−14.8 ± 21.8		3.1 ± 27.6		−3.4 ± 11.7	
Significance		$P \leq 0.001$		NS		NS	
Cardiac Output (liters/minute)	7.7 ± 2.4		5.8 ± 1.7		5.1 ± 1.4		4.9 ± 1.6
% Difference		−20.3 ± 25.1		−9.4 ± 9.7		−10.5 ± 19.5	
Significance		$P < 0.001$		$P < 0.001$		$P < 0.025$	
Stroke Volume (ml/minute)	83.8 ± 26.7		62.8 ± 19.7		54.9 ± 18.3		58.8 ± 30.6
% Difference		−21.4 ± 22.4		−9.1 ± 15.3		−8.5 ± 20.5	
Significance		$P < 0.001$		$P < 0.005$		$P < 0.05$	
Sys Vasc Res (dyne sec/cm^5)	700.8 ± 270.6		996.3 ± 349.4		1016.4 ± 395.6		1179.2 ± 478.2
% Difference		49.9 ± 43.8		5.7 ± 20.1		23.9 ± 30.1	
Significance		$P < 0.001$		NS		$P < 0.005$	
Pul Vasc Res (dyne sec/cm^5)	87.2 ± 30.9		102.1 ± 35.3		115.6 ± 45.4		115.4 ± 42.3
% Difference		22.8 ± 35.5		13.5 ± 17.9		10.0 ± 23.2	
Significance		$P < 0.001$		$P < 0.001$		NS	

between the specific gravity and specific heat of blood and distilled water. Using the estimated heat loss for blood at a room temperature of 18.3°C and a bypass flow of 2.5 L/M, the heat loss amounts to approximately 5 kilocalories/minute.

Discussion

The most significant point to be made from the data presented is that veno-venous bypass does not result in normal perfusion of the abdomen and lower extremities, probably because of inadequate venous return to the bypass pump. Despite continuous decreases in cardiac output and pump flow during bypass, cardiovascular compensatory mechanisms maintained arterial blood pressure.

Cardiac output and bypass flow decrease abruptly, due to decreased venous return, when the portal limb of the bypass circuit is clamped to allow completion of the portal vein anastomoses. However, continuous decreases in cardiac output and pump flow that occur throughout the bypass period can be related to decreased circulating blood volume that may result from blood loss, evaporation of fluid from exposed abdominal contents, and sequestration of fluid in the extravascular compartments of the abdomen and lower extremities. Pump flow rate dependent sequestration of fluid has been demonstrated based upon increases in osmotic and oncotic pressures, hematocrit, and sodium that could not be attributed to the administration of blood products or other colloids. The excellent inverse correlation between pump flow and changes in colloid osmotic pressure suggests increased filtration of fluid out of the vascular space into the extravascular volume of the abdomen and lower extremities. Belani et al. (14) have demon-

Table 4. Changes in Laboratory Values during Veno-Venous Bypass (mean ± standard deviation).

	Start	Unclamping	Difference	Different/Hr	n	Significance
PT (seconds)	15.8 ± 2.1	15.5 ± 1.6	−0.4 ± 1.2	−0.6 ± 1.9	39	NS
APTT (seconds)	60.5 ± 22.5	50.2 ± 16.8	−10.5 ± 18.4	−11.9 ± 26.1	39	$P < 0.005$
Platelets (cells/mm^3)	115.3 ± 67.1	120.4 ± 75.0	5.5 ± 48.2	10.3 ± 66.3	37	NS
Fibrinogen (mg/dl)	206.4 ± 66.7	208.8 ± 65.5	3.0 ± 19.9	4.48 ± 23.9	39	NS
Hematocrit (percent)	30.2 ± 4.6	31.9 ± 4.3	1.9 ± 1.9	2.3 ± 2.8	39	$P < 0.001$
Oncotic Pressure (mmHg)	13.0 ± 2.5	14.7 ± 2.6	1.7 ± 1.9	1.9 ± 2.5	26	$P < 0.001$
Serum Osmolality (mOsm/kg)	292.6 ± 17.8	294.6 ± 18.0	2.1 ± 5.1	2.8 ± 6.5	32	$P < .05$
Sodium (mEq/liter)	138.8 ± 5.4	139.9 ± 5.2	1.2 ± 2.1	1.4 ± 2.7	40	$P < .001$
Potassium (Eq/liter)	3.7 ± 0.8	3.6 ± 0.8	−0.1 ± 0.5	−0.03 ± 0.5	40	NS
Ionized Calcium (mM/liter)	0.96 ± 0.2	1.03 ± 0.3	0.07 ± 0.4	0.12 ± 0.48	40	NS
pH (units)	7.40 ± 0.06	7.39 ± 0.06	−0.01 ± 0.04	−0.017 ± 0.05	40	NS
Base (mEq/liter)	−2.9 ± 3.0	−4.2 ± 3.2	−2.1 ± 1.6	−1.7 ± 1.9	39	$P < .001$

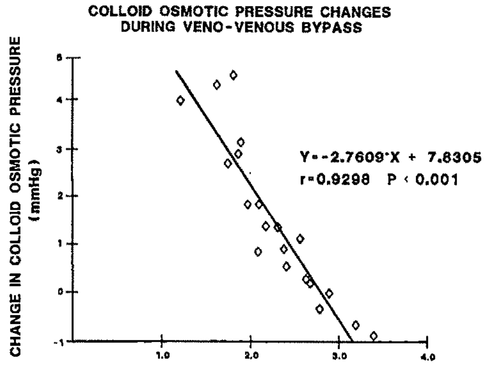

Figure 2. Changes in colloid osmotic pressure of the plasma as a function of the flow through the extracorporeal circuit.

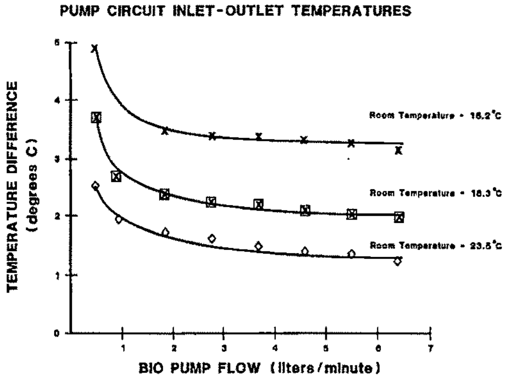

Figure 3. Temperature differences recorded from thermistors located at the inlet and outlet of the extracorporeal pump circuit, as a function of the bypass flow and room temperature. Water was pumped from a 13 liter constant temperature water bath through the bypass circuit and returned to the bath.

strated that infrahepatic vena cava pressure increases to 50 mm Hg without bypass. Peachey et al. (15) have found a mean increase of 26.9 mm Hg (range 19 mm Hg to 38.3 mm Hg) in infrahepatic caval pressure during bypass. The elevation in venous pressure is expected to be inversely related to pump flow, and, in the presence of maintained arterial pressure, increased filtration of fluid out of the vascular space is obligatory. Since pump flow is continually maximized by the operator, resistance to venous return to the pump must account for the increased venous pressure. Two factors may be responsible for decreased blood flow to the abdomen and lower extremities that result in increasing base deficit: 1) physiologic redistribution of cardiac output away from the gut and extremities as the cardiac output decreases; 2) decreased perfusion pressure across the abdomen and extremities resulting from increased venous pressure.

When an attempt was made to identify a dominant physiologic factor that determined bypass flow, no single or linear combination of measured parameters could adequately account for absolute flow or changes in bypass flow. Technical difficulties related

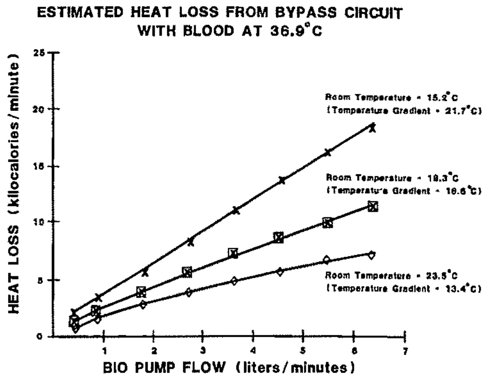

Figure 4. Calculated heat loss from the bypass circuit as a function of pump flow and room temperature, or temperature gradient between the circulating fluid and the room. Estimated heat loss for blood flowing through the bypass circuit was computed by substituting the specific gravity and specific heat of blood for distilled water. Since no consideration was given to the possibility that red cell motion may disturb the unstirred layer at the inner wall of the tubing, the heat loss may be underestimated.

to movement and position of venous cannulae may be significant determinants of pump flow in any given operation. However, a reasonable general hypothesis would be that pump flow is determined by cannula and vessel size that drain the venous system, along with regional mean circulatory filling pressure, just as cardiac output is related to mean circulatory filling pressure and the resistance to venous return (16).

Transient cardiovascular effects observed at the initiation of veno-venous bypass can be explained by cold volume loading of the heart, and possibly hemodilution of the coronary circulation. The well documented fall in heart rate that is proportional to decreasing temperature, and the ECG changes that accompany hypothermia, were reviewed by Popovic and Popovic (17). Interestingly, large ECG T wave changes typically associated with hyperkalemia were observed during this transient phase when potassium levels were not affected.

While it is not possible to determine directly, from the data presented above, whether all of the cardiovascular effects resulted from a transiently depressed myocardium or a combination of cardiac and vascular effects, a distinct vascular effect is unlikely. The time measured between the peak effects of the pump prime on the heart rate and the peak effects on the arterial pressure is only 4 seconds. Therefore, the pump prime probably could not have reached the smooth muscle cells of the arterioles or their neuroeffector junctions.

The statistically significant decrease in activated partial thromboplastin time (APTT) that could not be related to blood product administration, may be related to surface activation of factors V and VIII due to contact with the bypass tubing (18). There were, however, no clinically significant adverse affects upon the coagulation system due to the use of veno-venous bypass.

Heat loss from the bypass circuit could be inferred from the almost three times greater decrease in pulmonary artery temperature during bypass than during the preanhepatic phase. However, during the anhepatic phase, whole body metabolism could be expected to decrease by at least the metabolic component of the diseased liver. Decreases in whole body oxygen consumption during the anhepatic phase of the procedure of 25.7 percent (1) and 23.7 percent (19) have been reported. In addition, the cold donor organ is placed into the abdomen against the diaphragm while the anastomoses are completed, thus conducting a variable amount of heat from the body to the donor liver. Data acquired from the pump circuit and the constant temperature water bath experiments indicate that heat loss from the bypass circuit is dependent upon pump flow rate and the difference between the patient temperature and room temperature. Basal heat production in a 70 kg unanesthetized person is approximately 1.2 kilocalories per min (20). In the range of pump flows (1 to 3.5 L/M) used for veno-venous bypass, the estimated heat loss is always greater than basal heat production. Therefore, the heat loss from the bypass pump circuit always contributes to the core temperature decrease during the anhepatic phase. However, the absolute amount is dependent upon the patient's temperature and heat production, bypass flow, and room temperature.

Veno-venous bypass may provide enhanced cardiovascular stability (5) relative to procedures without bypass, but adequate perfusion of the abdomen and lower extremities and maintenance of circulating blood volume is not assured. Typically, during bypass, the cardiac output and pump flows continually decrease as a result of fluid extravasation from the vascular space to the interstitium. Data suggest that resistance to venous return to the bypass pump is the dominant factor influencing bypass flow and therefore the magnitude of interstitial fluid accumulation. Extrapolation of the data presented, as the pump flow approaches zero, suggests that maintenance of vascular volume and cardiovascular stability is assisted by the use of veno-venous bypass if adequate flow can be obtained. There are no clinically significant coagulopathies associated with the use of heparinless veno-venous bypass. Heat loss from the bypass circuit contributes to the increased rate of heat loss from the patient during the bypass period.

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Needle Direction Affects the Sensory Level of Spinal Anesthesia

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STIENSTRA R, van POORTEN F, KROON JW. Needle direction affects the sensory level of spinal anesthesia. Anesth Analg 1989;68:497–500.

The effect of the direction of the spinal needle on the sensory level of anesthesia was investigated. Three ml plain bupivacaine 0.5%, previously equilibrated to 37°C, were injected intrathecally in two groups of twenty patients, who were kept sitting for three minutes after injection. In patients in group 1 a paramedian approach was used with an angle between the spinal needle and the patient's back of 50° or less. In patients in group 2 a median or paramedian approach was used, the resultant angle between the spinal needle and the patient's back being between 70° and 100°. The differences between segmental levels of sensory loss between groups 1 and 2 (T 3.4 and T 5.1, respectively) and of temperature loss (T 2.6 and T 4.2, respectively) 30 minutes after injection of bupivacaine were statistically significant. It is concluded that a steep paramedian approach of the subarachnoid space with an angle of less than 50° results in a cephalad spread averaging about 1.6 segments greater than when the needle is in the perpendicular position.

Key Words: ANESTHETIC TECHNIQUES—spinal.

One of the factors that can affect the distribution of local anesthetic solutions in the subarachnoid space is the direction of the spinal needle through which injections are made. The possibility that the angle between the spinal needle and the longitudinal axis of the subarachnoid space may affect distribution of anesthetic solution is based on the assumption that if the anesthetic solution is injected through a spinal needle that is pointing in a cephalad direction, the resultant sensory level of blockade will be higher than if the needle is at a right angle with the longitudinal axis of the spinal canal (1).

The present study was undertaken to determine if in fact the direction of the spinal needle does affect the cephalad spread of plain bupivacaine 0.5% under controlled conditions.

Patients and Methods

Forty male patients (ASA physical status I-II) scheduled for urologic surgery under spinal anesthesia were randomly allocated to one of two groups, each group containing twenty patients. In all patients 3 ml plain bupivacaine 0.5% were injected intrathecally while they were in the sitting position; they were then kept sitting for 3 minutes after injection before being placed in the supine horizontal position. Dural puncture was performed in the L3-L4 interspace using a 25-gauge spinal needle. Patients in both groups received a solution that had been previously equilibrated to 37°C for at least 24 hours. Syringes used to administer the intrathecal solution were also equilibrated to 37°C. In patients in group 1 a paramedian approach was used, in which the angle between the spinal needle and the patient's back was at most 50°. In patients in group 2 a median or paramedian approach was used, in which the angle between the spinal needle and the patient's back was between 70° and 100°. The angle between the needle and the frontal plane was measured with a protractor. In patients in group 1 the point of needle entry was immediately lateral to the lower border of the processus spinosus of L4, in patients in group 2 the point of entry was level with the L3-L4 interspace. Thus in patients in group 1 entry in the subarachnoid space with the tip of the needle pointing cranially was achieved, whereas in patients in group 2 the position of the needle was more or less horizontal.

Premedication consisted of lorazepam 1 mg orally the night before surgery. Before induction of spinal anesthesia 500 ml Ringer's solution were administered by rapid intravenous infusion, followed, after

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Table 1. Patient Characteristics

	Group 1 (n = 20)	Group 2 (n = 20)	Delta 1-2 (P value)
Age (yr)	73 ± 1.86	72 ± 2.39	NS
Length (cm)	173 ± 1.43	177 ± 1.73	NS
Weight (kg)	72 ± 2.12	74 ± 2.34	NS

Group 1: Angle between spinal needle and longitudinal axis of spinal canal less than 50°. Group 2: Angle between spinal needle and spinal canal 70° to 100°.

NS, no statistically significant differences.

Data are means ± SEM.

Table 2. Segmental Levels of Loss of Sensation to Temperature (Temp) and Pinprick 30 Minutes After Injection

	Group 1 (n = 20)	Group 2 (n = 20)	Delta 1-2 P value
Temp (SEM)	T 2.6 (0.24)	T 4.2 (0.39)	≤0.01
Pinprick	T 3.4 (0.27)	T 5.1 (0.37)	≤0.002

Groups as defined in Table 1.

Mean values ± SEM. SEM in parentheses.

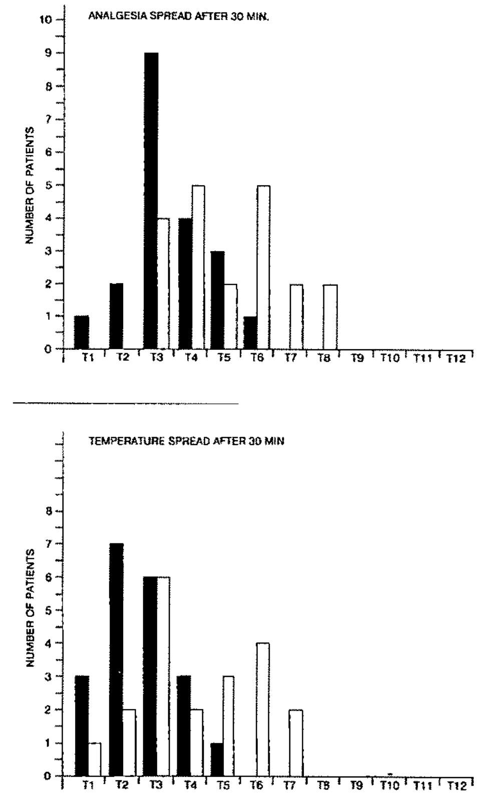

Figure 1. Segmental levels of loss of sensation to pinprick (analgesia spread) and temperature loss (temperature spread) 30 minutes after injection. The horizontal axis shows the thoracic segment at which temperature loss and loss of sensation to pinprick were measured; the vertical axis shows the number of patients. The differences between the two groups in segmental levels of loss of temperature and pinprick discrimination were statistically significant. ■ Group 1: Angle between spinal needle and longitudinal axis of spinal canal less than 50°. □ Group 2: Angle between spinal needle and spinal canal varying from 70° to 100°.

completion of the intrathecal injection, by 500 ml of a plasma expander at a slower rate. Bupivacaine solutions were injected at a rate of 0.2 ml/sec.

Blood pressure and pulse rate were measured before injection (T = 0) and 15 and 30 minutes after injection (T = 15 and T = 30) using an automatic cycling device (Dinamap). ECG was monitored continuously.

Measurement of the level of sensory changes was made 30 minutes after injection of the bupivacaine solution. Sensory loss was measured in the anterior axillary line by pinprick using a short bevelled 25-gauge needle. Temperature loss was measured using a cold bottle containing a frozen salt solution. The segment at which the patient was not capable of recognizing the temperature of the bottle as well as the segment at which there was loss of sensation to pinprick were recorded. Motor blockade was assessed 30 minutes after injection using a 0-3 scale as described by Bromage (2).

All punctures and observations were made by the authors under "observer blind" conditions.

The study was approved by the Ethics Committee of our institution and verbal consent was obtained from all patients.

Results are expressed as means ± SEM. Statistical analysis used the Wilcoxon test for matched pairs for intragroup variations and the Mann-Whitney-U test for intergroup comparisons. $P \le 0.05$ was taken indicative of statistically significant differences.

Results

The average angle between the spinal needle and the patient's back was 40° (range 20–45, SEM 1.4) in group 1 and 86° (range 70–90, SEM 1.2) in group 2. The differences between the two groups regarding age, length and weight were not significant (Table 1). The segmental level of temperature loss after 30 minutes averaged T 2.6 in group 1 and T 4.2 in group 2. The segmental level of loss of sensation to pinprick after 30 minutes averaged T 3.4 in group 1 and T 5.1 in group 2. Both these differences were statistically significant (Table 2). The ranges of levels are shown in Figure 1. All patients in both groups had complete motor blockade of the lower limbs after 30 minutes.

Systolic blood pressures decreased in both groups, decreases being significantly below baseline levels after 15 and 30 minutes. Baseline systolic blood pressures as well as the decreases in systolic blood pressure were similar in the two groups. The decrease in blood pressure necessitated the use of

Table 3. Systolic BP (mm Hg) and Heart Rate (beats/min) at Various Times (t) During and After Injection Into Subarachnoid Space

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Delta 1-2 (P value)
Systolic BP (t = 0)	139 (3.21)	135 (3.21)	NS
Systolic BP (t = 15)	115 (4.02) $P \leq 0.001$	118 (3.50) $P \leq 0.001$	NS
Systolic BP (t = 30)	122 (3.79) $P \leq 0.001$	118 (3.64) $P \leq 0.001$	NS
Heart rate (t = 0)	78 (3.70)	74 (1.80)	NS
Heart rate (t = 15)	78 (3.43) NS	74 (2.28) NS	NS
Heart rate (t = 30)	76 (2.70) NS	75 (2.42) NS	NS

Groups as defined in Table 1.
NS, no statistically significant differences.
Mean values ± SEM. SEM in parentheses.

ephedrine (15 mg intravenously plus 35 mg intramuscularly) in 7 patients in group 1 and in 4 patients in group 2.

The heart rates in either group showed no significant changes, nor were there significant differences in baseline heart rates between groups. Hemodynamic data are summarized in Table 3.

Operative conditions were good; none of the patients required analgeic supplementation. None of the patients developed postspinal headache.

Discussion

Many factors affect the intrathecal spread of anesthetic solutions (1). One of the major problems therefore in determining the influence of one factor is to effectively control the others. That this may be difficult if not impossible, is proven by the many controversies that still exist regarding the effect of some of these factors. In the case of bupivacaine 0.5% the difficulty in achieving effective control of all known and unknown determinants of intrathecal spread is clearly illustrated by the great variability of sensory spread as seen in the literature. Since it has been shown that equilibration of the plain solution of bupivacaine 0.5% to 37°C prior to intrathecal administration considerably reduces the variability of the ensuing sensory blockade (3), we administered a bupivacaine solution equilibrated to body temperature in order to minimize variability between the two groups of patients.

This study shows that changing the position of the spinal needle from a conventional more or less perpendicular entry into a reduced angle of entry of less than 50° results in a statistically significant increase in cephalad spread of 1.6 to 1.7 segments. It should be emphasized however that the clinical significance of this difference is quite limited compared to other factors affecting the sensory level of spinal anesthesia.

In a study comparing different directions of the bevel of the spinal needle in combination with different speeds of injection, Neigh et al. (4) found that the direction of the bevel of a conventional spinal needle had no effect on sensory spread. However, when using a Whitacre needle (where the fluid is ejected at 90° to the longitudinal axis of the needle), they found that injecting in a cephalad direction resulted in a higher cephalad spread as compared with injecting in a caudad direction or injecting through a conventional spinal needle. Although with conventional spinal needles the maximum acuteness of the angle between needle and longitudinal axis of the spinal canal is obviously limited, the result of reducing the angle of the needle with the tip pointing in a more cephalad direction is essentially the same as injecting through a Whitacre needle in a cephalad direction.

It has been shown that use of the plain solution of bupivacaine 0.5% is associated with a higher frequency of complete motor blockade of the lower limbs than the hyperbaric solution (5,6,7). Indeed, in our study all patients in both groups had complete motor blockade of the lower limbs after 30 minutes.

The decreases in systolic blood pressure as compared with baseline levels were statistically significant in each group, both after 15 and 30 minutes. The differences in decreases between the two groups were not significant. It should be noted however, that variation in both groups was large and that 11 patients received ephedrine. There were no statistical significant changes in heart rates.

In conclusion, when using the plain solution of bupivacaine 0.5% equilibrated to 37°C, using a steep paramedian approach of the subarachnoid space with an angle between spinal needle and longitudinal axis of the spinal canal of less than 50°, the resulting sensory blockade will average about 1.6 segments higher as compared with the conventional more or less perpendicular approach. The clinical significance of this finding is small.

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Interaction between Nitrous Oxide and Diazepam in the Mouse Staircase Test

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PRUHS RJ, QUOCK RM. Interaction between nitrous oxide and diazepam in the mouse staircase test. Anesth Analg 1989;68:501–5.

The interaction between nitrous oxide and diazepam was assessed in the mouse staircase test. In this paradigm, the numbers of rears (NR) (simultaneous standing on hindlegs and sniffing the air) and steps ascended (NSA) reflect anxiety and locomotor activity, respectively. Antianxiety drugs characteristically reduce NR but not NSA, while sedative drugs reduce both NR and NSA in generally parallel fashion. In this study, increasing concentrations of nitrous oxide alone produced progressively greater and statistically significant increases in NSA. Nitrous oxide alone had no significant effect on NR until, at a concentration of 75%, it decreased NR. Diazepam alone decreased NR equally and significantly at all doses. With certain combinations of concentration and dose, nitrous oxide enhanced the effect of diazepam on NR without altering NSA. These findings suggest that nitrous oxide can increase the antianxiety effect of diazepam without increasing its sedative effect in the mouse staircase paradigm.

Key Words: ANESTHETICS, GASES—nitrous oxide. HYPNOTICS, BENZODIAZEPINES—diazepam.

Nitrous oxide and the chemical family known as benzodiazepines, of which diazepam is representative, are both widely used in medical and dental anesthesia.

The sedative and analgesic effects of nitrous oxide have been recognized for years as being beneficial for induction of conscious sedation in dental patients (1–4) and to supplement general anesthetics during operative surgery (5). Inhalation of nitrous oxide produces an altered state of consciousness that can be characterized as sedated (6). Nitrous oxide analgesia occurs at concentrations of nitrous oxide that also produce sedation (7,8). It is likely that this analgesic effect contributes to the relaxed behavioral state of the patient.

The sedative and antianxiety effects of diazepam have also been utilized for intravenous sedation in dental patients (9–12) and for induction of anesthesia in surgical patients (13–17). Diazepam is effective in significantly reducing all forms of disruptive behavior and producing amnesia, e.g., when given rectally to young patients prior to dental treatment (18,19).

Despite the widespread use of both nitrous oxide and diazepam alone and in combination, knowledge of whether and how these two agents may interact and the consequences of such interaction remains incomplete For instance, it has been reported that, together, nitrous oxide and diazepam significantly reduce the rate of cerebral oxygen consumption in rats; however, neither drug alone has any appreciable effect on cerebral metabolic rate (20,21). Yet, in a subsequent study, nitrous oxide failed to potentiate diazepam inhibition of glycolysis in rat brain (22). Similarly, it has been reported that separately, nitrous oxide and diazepam reduce the convulsive effect of lidocaine in cats but that, in combination, there is no further reduction in the lidocaine seizures (23).

The purpose of the present investigation was to determine whether nitrous oxide and diazepam interact, using as a psychopharmacologic paradigm for detection of anxiolytic and/or sedative drug effect the mouse staircase test (24).

Methods

Experimental animals

Male ICR mice (Sasco/King Animal Laboratories, Oregon, WI), 20–30 g, were used in this research. Animals were used only once because, with repeated

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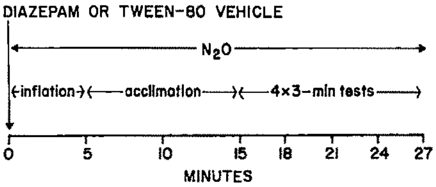

Figure 1. Time course of experimental protocol.

use, learning or familiarization with the staircase reduces the novelty of environment required for anxiety. The experiments described herein were reviewed and approved by an institutional animal care and use committee.

Mouse Staircase Test

Mice in groups of four were pretreated with one of several intraperitoneal (IP) doses of diazepam (2.0, 3.0, or 5.0 mg/kg) or with vehicle only. They were then placed inside a medium-sized, inflatable, polyethylene AtmosBag® glovebag (Sigma, St. Louis, MO) together with a polyvinyl chloride staircase (24). The glovebag was then sealed air-tight and varying proportions of nitrous oxide and oxygen delivered into the bag. In control experiments, the glovebag was left open to room air.

Following inflation of the glovebag—which required approximately five minutes—mice were allowed an additional 10 min acclimation to the nitrous oxide environment before testing (Fig. 1). No more than four mice were used per cage in an effort to standardize the nitrous oxide exposure time to approximately 15–24 minutes each at the time of the test. Mice were placed individually onto the lowest level of the staircase, facing away from the ascending steps. The number of rears (NR) and the number of steps ascended (NSA) during a three-minute period were counted. A rear was registered when the mouse rose on its hindlegs, either on the step or against the staircase wall, to sniff the air. A step was registered when the mouse completely ascended a step, placing all four paws on the step. In order to simplify observations, the number of steps descended were not counted.

Drugs

Drugs employed in this research included: nitrous oxide, U.S.P. and oxygen, U.S.P. (Bentley Welding, Milwaukee, WI), and diazepam (Valium®, Roche, Nutley, NJ). The gases were mixed and delivered into the glovebag at a constant inflow rate of 10 L/min, using a nitrous oxide/oxygen anesthesia machine (Adec, Newburg, OR). Diazepam was diluted in 0.3% Tween–80 solution. Control animals received injections of the Tween–80 vehicle without the diazepam. Both diazepam and vehicle were administered IP in injection volumes of 0.1 ml/10 g body weight. There were a total of sixteen groups of mice tested at different combinations of room air or nitrous oxide plus Tween–80 vehicle or diazepam (Table 1).

Statistical analysis of data

The data collected from different treatment groups were analyzed by analysis of variance (ANOVA) and Duncan's multiple range test.

Results

Table 2 depicts the interaction between increasing concentrations of nitrous oxide (25%, 50%, and 75% plus room air control) and increasing doses of diazepam (2.0, 3.0, and 5.0 mg/kg plus Tween-80 vehicle control) in the mouse staircase test. Administered alone (i.e., in the absence of diazepam), nitrous oxide produced a statistically significant concentration-related increase in NSA above NSA values observed in the absence of diazepam while breathing room air. Nitrous oxide alone significantly reduced NR only at the 75% level. Administered alone (i.e., in the absence of nitrous oxide), diazepam significantly and equally decreased NR at all doses, accompanied by smaller but non-significant reductions in NSA.

Lower test concentrations of nitrous oxide generally had no effect on NSA in the presence of diazepam: when 25% nitrous oxide was added to each dose of diazepam, the mean NSA remained unchanged; when 50% nitrous oxide was added, there was further reduction in NSA only in the 5.0 mg/kg diazepam group ($P < 0.05$); and when 75% nitrous oxide was added, there was further reduction in NSA in the presence of all three doses of diazepam ($P < 0.05$). On the other hand, the NR-lowering effect of diazepam was more sensitive to influence by nitrous oxide: when 25% nitrous oxide was added, there was further reduction only in NR in the 3.0 mg/kg diazepam group ($P < 0.05$); when 50% nitrous oxide was added, there was further reduction in NR in the 3.0 and 5.0 mg/kg diazepam groups ($P < 0.05$); and when 75% nitrous oxide was added, there was further reduction in NR in the presence of all three doses of diazepam ($P < 0.05$). Table 2 also indicates that certain concentrations of nitrous oxide can increase

Table 1. Drug Combinations Used in Each Treatment Group

Nitrous Oxide Concentration	Dose of Diazepam			
	Tw80 Vehicle	2.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Room Air	GP #1 (37) Room Air Tw80 Vehicle	GP #2 (19) Room Air 2.0 mg/kg DZ	GP #3 (35) Room Air 3.0 mg/kg DZ	GP #4 (19) Room Air 5.0 mg/kg DZ
25% N_2O	GP #5 (19) 25% N_2O Tw80 Vehicle	GP #6 (18) 25% N_2O 2.0 mg/kg DZ	GP #7 (19) 25% N_2O 3.0 mg/kg DZ	GP #8 (19) 25% N_2O 5.0 mg/kg DZ
50% N_2O	GP #9 (20) 50% N_2O Tw80 Vehicle	GP #10 (20) 50% N_2O 2.0 mg/kg DZ	GP #11 (18) 50% N_2O 3.0 mg/kg DZ	GP #12 (17) 50% N_2O 5.0 mg/kg DZ
75% N_2O	GP #13 (19) 75% N_2O Tw80 Vehicle	GP #14 (19) 75% N_2O 2.0 mg/kg DZ	GP #15 (18) 75% N_2O 3.0 mg/kg DZ	GP #16 (18) 75% N_2O 5.0 mg/kg DZ

Abbreviations: GP, Group; Tw80, Tween–80; DZ, diazepam; N_2O, nitrous oxide.

Table 2. Numbers of Steps Ascended and Rears in Different Treatment Groups

Nitrous Oxide Concentration	Dose of Diazepam			
	Tw80 Vehicle	2.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Influence on NSA				
Room Air	25.8 ± 1.3	19.1 ± 3.6	18.2 ± 3.2	20.7 ± 3.5
25% N_2O	40.8 ± 2.6a	20.6 ± 3.4	19.2 ± 2.7	24.4 ± 4.1
50% N_2O	44.2 ± 1.8a	24.0 ± 4.7	19.4 ± 5.2	9.5 ± 3.7ab
75% N_2O	54.6 ± 4.7abc	6.2 ± 2.4abc	6.6 ± 2.5abc	8.6 ± 3.4ab
Influence on NR				
Room Air	19.6 ± 1.4	4.7 ± 0.8	7.4 ± 1.4	5.2 ± 1.0
25% N_2O	30.1 ± 1.8a	4.1 ± 0.8	3.1 ± 0.6a	4.4 ± 0.8
50% N_2O	27.1 ± 1.8a	7.0 ± 1.7	2.5 ± 0.8a	1.2 ± 0.4ab
75% N_2O	12.5 ± 2.2abc	0.9 ± 0.3abc	0.9 ± 0.3a	1.0 ± 0.4ab

Abbreviations: NSA, number of steps ascended; NR, number of rears; Tw80, Tween–80; DZ, diazepam; N_2O, nitrous oxide. Numbers indicate the mean NSA or NR ± SEM of each group. Significance of difference: a, $P < 0.05$, compared to group receiving same dose of DZ in Room Air; b, $P < 0.05$, compared to same dose of DZ in 25% N_2O; and c, $P < 0.05$, compared to group receiving same dose of DZ in 50% N_2O.

the NR-lowering effect of diazepam without increasing the NSA-lowering effect of diazepam (i.e., 25% nitrous oxide × 3.0 mg/kg diazepam, 50% nitrous oxide × 3.0 mg/kg diazepam).

Figure 2 is a graphic representation of these interactions of nitrous oxide and diazepam on NSA and NR.

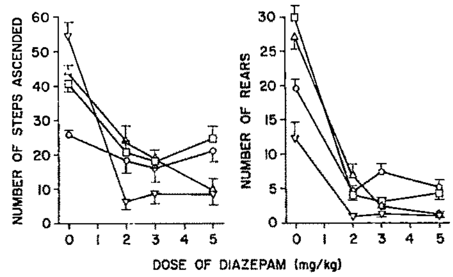

Figure 2. Effects of increasing doses of diazepam upon number of steps ascended (left) and number of rears (right) in groups of mice while breathing: room air ○; 25% nitrous oxide □; 50% nitrous oxide △; and 75% nitrous oxide ▽. Each point indicates the mean number of steps ascended or of rears of 17–37 mice per group. Vertical bars indicate the standard errors of the mean.

Discussion

The rationale for the mouse staircase test is based on some 20 years of psychological testing. Lat (25) suggested that rearing activity in rats was indicative of increased vigilance. In the early moments of testing, such activity reflects desire of the animal to escape and is distinguished from subsequent exploratory locomotor activity (26). Thiebot and associates (27,28) introduced the staircase test, in which a rat, placed into an unfamiliar staircase, initially exhibits exploratory activity in the form of step-climbing and anxiety in the form of rearing and sniffing. This test was subsequently modified for mice by Simiand et al. (24), who showed that benzodiazepines as well as nonbenzodiazepine anxiolytic drugs selectively reduce NR at doses that have little or no effect upon NSA; at higher doses, however, NSA is also reduced due to central nervous system depression (sedation). In contrast, non-anxiolytic drugs, such as tricyclic antidepressants or anti-psychotic drugs, simultaneously reduce both NR and NSA. The validity of NR as a measure of anxiety was recently tested by screening drugs with various activities at the benzodiazepine receptor (29): at low doses, benzodiazepine receptor agonists (diazepam, chlordiazepoxide, midazolam) significantly reduce NR; a benzodiazepine receptor inverse agonist (noreleagnine) increases NR without effect upon NSA; and a benzodiazepine receptor antagonist (flumazenil), which alone has no effect on NR or NSA, reverses the NR effects of both agonists and inverse agonists.

In the present investigation, diazepam reduced NR without reducing NSA. According to the paradigm, this reflects an anxiolytic drug effect. Our findings also show that nitrous oxide increased NSA in concentration-related fashion and had no influence upon NR except at 75%. Superficially, this might seem to imply that nitrous oxide has no anxiolytic effect in the staircase test. However, it is likely that the increased NSA may be due to an opioid-mediated locomotor stimulatory effect of nitrous oxide in mice (30–32), an effect that might mask the antianxiety activity of nitrous oxide in this particular paradigm. But in mice in which opioid receptors are blocked by naloxone, nitrous oxide produces a concentration-dependent reduction in NR (32). A response similar to an increase in NSA, one of agitation, has been observed by the authors in humans, particularly in young children and mentally handicapped persons, especially during their initial exposure to nitrous oxide; it is noteworthy that diazepam reduced this response at all doses.

Our results indicate that exposure to either 25% or 50% nitrous oxide increases the ability of 3.0 mg/kg diazepam to reduce NR without further suppression of NSA. On the other hand, 50% and 75% nitrous oxide increased the ability of 5.0 mg/kg diazepam to reduce NR concomitant with greater suppression of NSA. We interpret these findings to mean that, in the mouse staircase paradigm, exposure to nitrous oxide is capable of increasing the anxiolytic effect of diazepam at certain dose combinations without increasing the level of sedation. This finding may have clinical implications for patient treatment when such a response is desirable.

The mechanism of the nitrous oxide-diazepam interaction may be due to both drugs acting at the same site. The NR-lowering effects of both benzodiazepines and nitrous oxide in the mouse staircase test are reversed by flumazenil (29,33). It may also be conceivable that opioid activity somehow influences the affinity of binding sites for benzodiazepine drugs. Or, pharmacokinetic mechanisms may be involved. Identification of the mechanisms responsible for the increased antianxiety effect of diazepam in the presence of nitrous oxide requires further study.

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Effect on Airway Resistance of Ketamine by Aerosol In Guinea Pigs

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ROCK MJ, REYES DE LA ROCHA S, LERNER M, BRACKETT D, WILSON MF. Effects on airway resistance of ketamine by aerosol in guinea pigs. Anesth Analg 1989;68:506–10.

The effect of aerosolized ketamine hydrochloride was investigated by measuring airway resistance with a two-compartment plethysmograph in guinea pigs challenged with histamine. In the first phase of the study, treatment with ketamine prior to histamine challenge did not protect against elevation of airway resistance. In the second phase of the study, ketamine inhalation after histamine challenge did not significantly diminish airway resistance. Aerosolized ketamine is not recommended for use in human subjects with asthma.

Key Words: ANESTHETICS, INTRAVENOUS—ketamine. LUNGS, bronchi.

Previous case reports in humans have advocated using intravenous ketamine hydrochloride in asthmatics who do not respond to conventional therapy (1,2). The mechanism of action of ketamine is not completely known. However, ketamine increases catecholamine levels (3), which may cause relaxation of bronchial smooth muscle. The basis of the smooth muscle relaxant effect of ketamine comes from observations in vitro of tracheal chains (excised segments of trachea) isolated from guinea pigs (4–6). In these studies the tracheal chains were directly bathed in ketamine solution. This type of study is an important first step in investigating the possible clinical usefulness of ketamine, but further studies need to be performed with live animals. Therefore in our study, we investigated the effect of aerosolized ketamine on airway resistance in guinea pigs challenged with aerosolized histamine.

Materials and Methods

Equipment and animals

Female Hartley guinea pigs (SASCO Inc., Nebraska), weighing approximately 340 grams, were studied in a two-compartment body plethysmograph; the equipment and techniques used were previously described by Pennock, et al. (7). The double-body plethysmograph consisted of two air-tight plexiglass chambers, referred to as the head box and the body box. The two boxes were separated by a rubber dental dam and a collar through which the guinea pig's neck fits, thus maintaining the air-tight seal between the two compartments. Both of the boxes were monitored by Validyne MP-45 pressure transducers connected to Validyne CD 15 carrier demodulators and were connected to a Tetronix model 4701 multiplexer and a Tektronix model 613 oscilloscope. During normal breathing, pressure changes in the body box and the head box were displayed simultaneously on the oscilloscope as two sine waves. An increase in airway resistance produced a time delay in the pressure changes between the body box. When the head and body box transducers were connected 180° out of phase, the oscillating plot consisted of a straight line 45° to the horizontal. Increases in airway resistance produced a lag in the time of the thoracic pressure (body box) behind the mouth pressure (head box). This caused a phase shift resulting in the formation of a lissajous loop (see Fig. 1).

The measurement of this loop and the respiratory frequency were used to calculate the value $R_{aw} \times C_a$ (R_{aw} = airway resistance, C_a = compliance of air in head box), which was also called the $RC \times 10^{-3}$ value, and was calculated by the formula:

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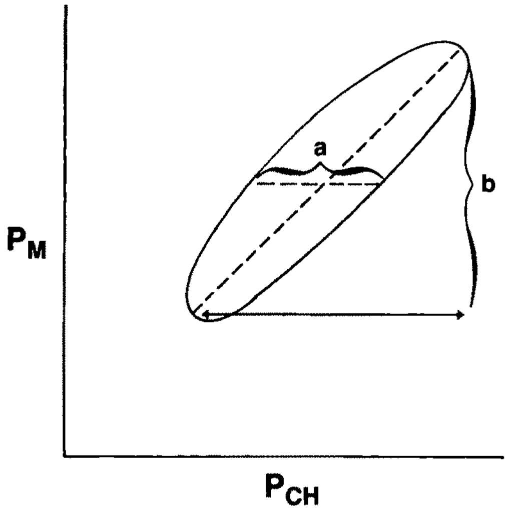

Figure 1. Schematic lissajous loop of mouth (Pm) vs chest (PCH) pressure. "a" horizontal distance between both sides of the loop. "b" length of the loop.

$$R_{aw} \times C_a = RC \times 10^{-3}\ (\text{sec}) = \left[\frac{(f)\ (a)}{\sqrt{(b^2 - a^2)}\ 105.5}\right] \times 1000$$

The value for "a" represents the horizontal distance between both sides of the loop. The value for "b" is the measure of the length of the loop. Both were measured with a micrometer caliper from the lissajous loop presentation on the oscilloscope. The value for "f" was obtained from the oscilloscope presentation of the respiratory rate oscillation from the body box by measuring the distance from peak to peak of five sine waves. The equation was multiplied by 1000 to obtain a number not in decimal format. The results were referred to as the RC × 10^{-3} value. The additional parameter, respiratory rate, was calculated by using the measured "f" in the equation:

$$\underset{\text{(respiratory rate)}}{\text{breaths per minute}} = \frac{792}{f}$$

The number 792 represented the measure of the screen of the oscilloscope.

The head box was connected by manually operated valves to two types of nebulizers. A Monaghan 670 ultrasonic nebulizer was used to generate the aerosolized solution to be studied in the droplet size range of 1 to 8 μm. The aerosol was generated into an air flow of 1.9 LPM. A Hudson model 1700 updraft nebulizer was used to produce a saline aerosol to flush the studied solution out of the head box. The construction of the mechanism was such that, because of the requirement of a sealed system, no measurement requiring head box (RC × 10^{-3}) pressure could be made during aerosolization of the solution nor during saline flush. In this study, we measured airway resistance as a change from the baseline levels.

This study was approved by the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

Phase One

Phase one of the study was designed to assess the protective effect of ketamine against a histamine challenge. A positive control consisted of a known bronchodilator, isoproterenol. A negative control consisted of saline solution. Six guinea pigs were studied; on different study days, each guinea pig crossed over between the pretreatment with saline versus ketamine versus isoproterenol. Each guinea pig was subjected to only one challenge per day.

The guinea pig was placed in the two-compartment plethysmograph with a rubber seal about the neck, thus separating the head compartment from the body compartment. Baseline readings of airway resistance were measured each minute for five minutes. The head compartment was then exposed to the aerosolized study solution. The study solutions consisted of 10 ml of saline, 10 ml of ketamine (10 mg/ml), and 10 ml of isoproterenol (100 mg/20 ml) (8). The saline and ketamine were aerosolized for one minute, followed by a 30-second flush with room air. The isoproterenol was aerosolized for 30 seconds, followed by a 30-second flush with room air.

After the study solution was aerosolized, airway resistance was measured each minute for another five minutes. The guinea pigs were then challenged with aerosolized histamine solution, 10 ml of 400 μg/ml concentration (8). This was aerosolized for 30 seconds, followed by a 30-second flush of room air. Airway resistance was then measured each minute for the next 15 minutes. The peak airway resistance occurred within the first six minutes after histamine challenge. The amount of study solutions delivered were measured by the weight difference of the nebulizer cup before and after the aerosol treatment (Table 1).

Phase Two

Phase two of the study was designed to assess the effect of ketamine after the animals had already experienced increased airway resistance from aerosolized histamine. Baseline airway resistance was measured for 5 minutes. The animals were then exposed

Table 1. Amount of Solutions Delivered by Aerosol During Phase One of The Study

	Day 1		Day 2		Day 3	
Animal No.	Histamine (μg)	Ketamine (mg)	Histamine (μg)	Ketamine (mg)	Isoproterenol (mg)	Histamine (μg)
1	600		320	14	3.5	400
2	520	27	360		7	600
3	400		400	15	5	460
4	600	24	360		5	400
5	440		360	17	5	400
6	480	22	320		5.5	440
Mean ± SD	506.3 ± 82.62	24.3 ± 2.51	353.3 ± 30.11	15.3 ± 1.52	5.1 ± 0.96	450 ± 77.71

Table 2. Amount of Solutions Delivered by Aerosol During Phase Two of the Study

	Day 1		Day 2		Day 3	
Animal No.	Histamine (μg)	Ketamine (mg)	Histamine (μg)	Ketamine (mg)	Histamine (μg)	Isoproterenol (mg)
1	400		480	21	640	9
2	600	24	600		680	9.5
3	600		560	25	560	10
4	520	26	600		560	7.5
5	640		560	22	600	9.5
6	520	29	520		600	9
Mean ± SD	546 ± 86.40	26.3 ± 2.51	553.3 ± 46.76	22.6 ± 2.08	606.6 ± 46.76	9 ± 0.86

to aerosolized histamine solution for 30 seconds, followed by a 30-second flush of room air. The guinea pigs were in respiratory distress after the histamine challenge as evidenced both by increased respiratory rate and visual observation of intercostal retractions. Measurements of airway resistance were significantly elevated from baseline. The study solutions (saline, ketamine, or isoproterenol) were administered in the same amount as in phase one and were aerosolized two to four minutes after the histamine aerosol. Each solution was aerosolized for one minute, followed by a 30-second flush of room air. Airway resistance was then measured each minute for a total of 15 minutes after the histamine was started. As in phase one, each guinea pig was subjected to only one challenge per day, and amounts of solution delivered were measured by weighing the nebulizer cup before and after the treatment (Table 2).

Statistical Methods

Because the variances among the three groups were unequal, a nonparametric test, the Kruskal-Wallis statistic, was utilized (9). If the Kruskal-Wallis statistic was significant ($P < 0.05$), then pairwise comparisons between the three groups was performed using the Wilcoxon rank sum test (10). Because three groups were being compared (saline vs ketamine, saline vs isoproterenol, ketamine vs isoproterenol), statistical significance was defined by the Bonferroni correction for multiple comparisons, defined as $P < 0.05/3$, or the 1.67% level.

Results

Table 3 summarizes the data from phase one of the study. The airway resistances of the saline pretreated group were much larger compared with the other two groups, and the Kruskal-Wallis statistic was significant ($P < 0.025$), thus indicating that there was a difference among the three groups. To identify which group was responsible for this difference, pairwise comparisons with the Wilcoxon rank sum test were performed. Only the isoproterenol group compared to the saline group was statistically significant ($P < .0167$). Although the airway resistances between the saline and ketamine group were not statistically significant (statistical significance was approached with $P = 0.032$), it is notable that four of the six guinea pigs pretreated with ketamine had lower peak airway resistances than when pretreated with saline.

Table 4 summarizes the data from phase two of the study. The four plus symbols signify that the animals were in too much distress to measure their airway resistance effectively. The post-treatment airway resistances were not statistically significant among the three groups.

Table 3. Relative Peak Airway Resistance After Pretreatment With Saline, Ketamine, and Isoproterenol Followed by Histamine Challenge

	Saline	Ketamine	Isoproterenol
Guinea pig #1	18.2	26.8	0.0
Guinea pig #2	35.8	12.4	2.1
Guinea pig #3	65.1	17.9	18.3
Guinea pig #4	92.1	3.3	3.7
Guinea pig #5	6.7	6.9	4.0
Guinea pig #6	34.7	15.9	7.8
Mean ± 1 SD (N = 6)	42.1 ± 28.7	13.87 ± 7.64	5.98 ± 5.99

Table 4. Peak Airway Resistance After Histamine Challenge, and After Treatment With Saline, Ketamine, and Isoproterenol

	Histamine/Saline		Histamine/Ketamine		Histamine/Isoproterenol	
Guinea pig #1	++++	11.5	21.7	3.3	8.8	1.0
Guinea pig #2	9.9	13.4	19.6	24.2	6.4	1.9
Guinea pig #3	29.8	2.3	++++	0.0	8.7	5.1
Guinea pig #4	9.5	3.2	++++	0.0	17.4	2.8
Guinea pig #5	44.8	19.5	++++	0.9	++++	3.2
Guinea pig #6	++++	6.2	++++	2.3	35.7	1.9
Mean ± 1 SD (N = 6)		9.35 ± 7.44		5.12 ± 9.44		2.65 ± 1.4

By their outward appearance, the animals' level of consciousness did not appear to change during either phase of the study, nor was excessive production of mucus observed following aerosolized ketamine.

Discussion

Aerosol therapy is an important method of treatment for reversible airway obstruction. It has a number of advantages over oral, subcutaneous, and intravenous routes of drug delivery. First, the onset of action is usually rapid; second, small doses may be used; lastly, the incidence of systemic side effects is low (11). It has become routine to administer such drugs as beta adrenergic agonists, anticholinergics, cromolyn sodium, and corticosteroids by aerosolization. Inhalation techniques using other drugs not conventionally employed for asthma have been investigated, including agents such as prostaglandins E (11), vasoactive intestinal peptide (12), and calcium channel blockers (13).

Intravenous ketamine clinically relieves airway obstruction in asthmatic patients, and its effects on airway resistance in humans have also been measured. Huber et al. (14) compared airway resistance before and after ketamine infusion in normal subjects and in patients with asthma. They found that ketamine did not appreciably affect airway resistance in patients with our pulmonary disease. However, in patients with pulmonary dysfunction involving increased airway resistance, ketamine was usually effective in reducing this resistance. Furthermore, the response to ketamine was directly proportional to the degree of preexisting bronchial obstruction: the more severe the obstruction and the higher the airway resistance, the more pronounced was the reduction of airway resistance.

The mechanism by which ketamine produced bronchodilation is open to speculation, and perhaps it is different from that of conventional bronchodilators. Ketamine structurally does not resemble drugs such as epinephrine or isoproterenol. Therefore, it is questionable that ketamine acts on the beta receptors. However, Hirshman and colleagues (15) demonstrated that induced bronchospasm in dogs could not be reversed by ketamine during beta blockade. This suggests that, at least partially, sympathetic receptors are involved in ketamine bronchodilation. Ketamine also depresses the vagal pathway, and this effect may allow reversal of irritant-receptor induced bronchoconstriction (16). Ketamine appears to increase endogenous cathecholamine levels by a cocaine-like action blocking the reuptake of norepinephrine into the presynaptic sympathetic neurons (17). A possibly more important mechanism of action of ketamine could be a direct smooth muscle relaxant effect (4–6). Vitkun et al. (18) studied the in vitro airway response to ketamine in the guinea pig. They found ketamine to be effective in producing relaxation of smooth muscle only when the basal tone was increased by pretreating the airway preparation with histamine or methacholine. The response was also dose dependent. The author suggested that bronchial relaxation produced by ketamine was due to a combination of competitive and non-competitive antagonism between ketamine and the bronchoconstrictors. The non-competitive effect was found to be more pronounced.

There are several drawbacks in the use of intravenous ketamine in asthmatics. In addition to anesthetizing the patient and causing cardiovascular stimulation, ketamine administered intravenously can cause postanesthesia emergence reactions that are particularly undesirable. Most importantly, although laryngeal and pharyngeal reflexes are allegedly retained, cases of aspiration have been reported (19,20). Therefore, it is recommended that intravenous ketamine be given only to intubated patients (2).

The purpose of this study was to investigate the effects of ketamine when given by aerosolization. It was anticipated that by this method the abovementioned side effects could be avoided and ketamine could potentially be given to patients that are not intubated. In phase one of the study, ketamine did not protect against elevation of airway resistance to a statistically significant degree, but four of the six animals had a lower peak airway resistance compared with the saline control. The failure to obtain statistical significance may be due to the small sample size. In phase two of the study, neither aerosolized ketamine nor isoproterenol were found to significantly decrease airway resistance following histamine challenge. Previously, it had been established that the administration of isoproterenol resulted in adequate bronchodilation in histamine-challenged guinea pigs as measured in our animal plethysmograph (7,8). Since our positive control, isoproterenol, did not result in a statistically significant diminution of elevated airway resistance in the current study, the findings in phase two may be invalid. Our study of examining airway resistance in the whole live animal was a logical extension of previous investigations in which the effects of ketamine on isolated excised tissues was studied in vitro. Delivering the same amount of study solution and histamine to the animals proved to be technically difficult in our study. Although the same amount of solution was placed in the nebulizer cup and the length of aerosolization was uniform among treatment groups, the amount of "delivered" solution varied up to 100%. ("Delivered" solution was determined by the difference in the weight of the nebulizer cup before and after aerosolization.) Although statistically significant results were not obtained, we believe aerosolized ketamine deserves further study. A dose-response curve for ketamine needs to be generated, and aerosolized ketamine could also be comprehensively evaluated in animal IgE-mediated models of asthma.

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Isoflurane Anesthesia in Sandhill Cranes (*Grus canadensis*):

Minimal Anesthetic Concentration and Cardiopulmonary Dose-response During Spontaneous and Controlled Breathing

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LUDDERS JW, RODE J, MITCHELL GS. Isoflurane anesthesia in Sandhill cranes (*Grus canadensis*): Minimal anesthetic concentration and cardiopulmonary dose-response during spontaneous and controlled breathing. Anesth Analg 1989;68:511–16.

Information on species differences in responses to inhalation anesthetics has been established in a variety of mammalian and non-mammalian species, but comparable studies have not been reported in birds. The purpose of this study was to determine minimal anesthetic concentration and cardiopulmonary concentration-response effects of isoflurane in Sandhill cranes. Six cranes were anesthetized with isoflurane in oxygen. Gases sampled through a polyethylene tube inserted to the distal end of an endotracheal tube were used for measurements of isoflurane concentrations using an infrared gas analyzer. Body temperature was maintained at 40 ± 0.5°C. The minimal anesthetic concentration for isoflurane was determined during spontaneous ventilation, and concentration-response data were collected at 1, 1.5, and 2.0 times the minimal anesthetic concentration. Concentration-response data were repeated during mechanically controlled breathing with $PaCO_2$ maintained between 27 and 35 mm Hg. The minimal anesthetic concentration for isoflurane was 1.34 ± 0.14 vol% (mean ± SD). Concentration-dependent respiratory depression during spontaneous breathing was evidenced in all cranes by an increase in $PaCO_2$. Isoflurane induced apnea in two of the cranes during spontaneous ventilation at 2 times the minimal anesthetic concentration. As the concentration of isoflurane was increased, mean arterial blood pressure decreased during both spontaneous and controlled ventilation. Mean arterial blood pressure was higher during controlled ventilation than during spontaneous ventilation. The minimal anesthetic concentration for isoflurane in Sandhill cranes is similar to values for isoflurane minimal anesthetic concentration in mammals. Isoflurane has dose-dependent effects on cardiopulmonary function qualitatively similar to those observed in mammals.

Key Words: ANESTHESIA—avian. ANESTHETICS, VOLATILE—isoflurane. POTENCY, ANESTHETIC—isoflurane.

The minimum alveolar anesthetic concentration that produces anesthesia in mammals exposed to noxious stimuli is referred to as MAC. Because it is a measure which provides a description of concentration and effect, it can be used to quantify factors that influence anesthetic requirements, and it is a term that can be applied equally to all inhalation anesthetics (1). Although MAC has been determined for a number of inhalation anesthetics in a variety of mammalian and non-mammalian species, it has not been reported for most inhalation anesthetics in avian species (2), and should be.

The avian pulmonary system, consisting of parabronchial lungs and air sacs that mechanically serve as bellows to the lungs, is anatomically and physiologically different from the mammalian pulmonary system. These differences have led to speculations that birds and mammals respond differently to inhalation anesthetics. Because of the lack of information on the effects of inhalation anesthetics in birds, the aim of this study was to determine the minimal anesthetic concentration and cardiopulmonary concentration-response effects of isoflurane in birds, specifically Sandhill cranes, a non-endangered species of crane.

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Methods

These studies were approved by the Animal Care Committee of the School of Veterinary Medicine, University of Wisconsin, Madison, Wisconsin.

Six young Sandhill cranes (7 to 9.5 months; 4.0 ± 0.3 kg) were used in this study. The birds were fasted the night prior to study. Anesthesia was induced with isoflurane in oxygen delivered from an out-of-circuit, agent specific, flow and temperature compensated vaporizer (Fortec, Fraser Harlake, NY). The isoflurane was administered through a mask attached to a non-rebreathing circuit. After induction, each bird was intubated with a long, uncuffed endotracheal tube with its tip located at the thoracic inlet. Each bird was positioned in dorsal recumbency and, using aseptic surgical technique, the ulnar artery was exposed for catheterization. A sterile catheter was inserted into the ulnar artery for measuring arterial blood pressure and for sampling arterial blood for measurement of pH, $PaCO_2$, and PaO_2. Arterial blood pressure was continuously monitored (P23id Transducer, Gould Inc, OH) and displayed on a physiologic recorder (Gould Recorder 2600S, Gould Inc, OH). Arterial blood was collected and immediately analyzed at 37°C for pH, $PaCO_2$, and PaO_2 (ABL 2, Radiometer, Denmark). All blood-gas data were corrected to body temperature using standard mammalian correction factors. A venous catheter was inserted percutaneously into the right jugular vein for infusion of physiologic saline (0.9% sodium chloride, 5 $ml \cdot kg^{-1} \cdot hr^{-1}$), and a lead II ECG was recorded throughout the experiment. Each bird was placed in lateral recumbency to minimize impairment of sternal motion and pulmonary ventilation (3). A temperature probe was inserted into the esophagus to the level of the heart for measuring body temperature which was maintained at 40.0 ± 0.5°C with circulating water blankets and by varying environmental temperature. A pneumotachograph was used to measure respiratory rate (f) and tidal volume (V_t) from which minute ventilation (V_{min}) was derived. Gas was sampled from the distal end of the tracheal tube and analyzed for isoflurane concentration with an infrared gas analyzer (Beckman Medical Gas Analyzer LB-2, Beckman Instruments, Inc, CA) calibrated for isoflurane. The analyzer was frequently calibrated during each study, and the aspiration flow rate was set at 500 ml/min. To prevent mixing of inspired isoflurane with end-tidal isoflurane, gas was not continuously sampled from the end of the endotracheal tube; gas was only sampled during the expiratory phase of the respiratory cycle. End-tidal isoflurane concentration was determined as the average of three samples taken every other breath. Measurements of respiratory frequency and tidal volume were made when gas was not aspirated from the end of the endotracheal tube by the gas analyzer.

The minimal anesthetic concentration for isoflurane was determined during spontaneous ventilation, in a manner similar to MAC determinations in mammals (4); for the sake of convention, minimal anesthetic concentration will be abbreviated as MAC (see Discussion). After induction and instrumentation, a given concentration of end-tidal isoflurane was maintained constant for at least 15 minutes to assure equilibration of isoflurane in the lungs with that in arterial blood and brain. At the end of the equilibration period, arterial blood was collected for analysis of pH, $PaCO_2$, and PaO_2. A standardized noxious stimulus was used in all experiments to determine MAC. The jaws of a hemostat were fully clamped for their entire length to the junction of a toe and toe-web for a period of 1 minute. If there was no motor response to stimulation, such as lifting of the head and neck, flapping of the up wing, or kicking of the legs, the end-tidal isoflurane concentration was reduced 20%. Fifteen minutes was again allowed for equilibration at a constant end-tidal isoflurane concentration, arterial blood was collected for analysis, and the noxious stimulus was repeated. Additional decrements of the end-tidal isoflurane concentration were made (10 to 20% each time) until a purposeful movement occurred in response to the stimulus. The isoflurane concentration was then increased 10% and, following 15 minutes of equilibration at a constant end-tidal concentration, the stimulus was repeated. MAC was taken to be the isoflurane concentration half-way between that allowing and that preventing movement.

Immediately after determination of MAC and with the cranes breathing spontaneously, concentration effects of isoflurane on cardiopulmonary function were measured at 1, 1.5, and 2.0 times the MAC. The order of study was randomized. Each crane was held constant at 1, 1.5, or 2.0 times its MAC for a 15-minute equilibration period. At the end of the equilibration period, arterial blood was collected for analysis of pH, $PaCo_2$, and PaO_2, and blood pressure, ventilation, and ECG were recorded. The cranes were then allowed to recover. One-and-a-half months later the cranes were again anesthetized with isoflurane, instrumented as described above, and concentration-response studies repeated during controlled ventilation at multiples of MAC previously determined for each bird.

Table 1. Dose-response Effects of Isoflurane in Sandhill Cranes During Spontaneous and Controlled Ventilation

	1.0 × MAC		1.5 × MAC		2.0 × MAC	
	Spontaneous	Controlled	Spontaneous	Controlled	Spontaneous	Controlled
	(n = 6)	(*n* = 5)	(*n* = 6)	(*n* = 5)	(*n* = 4)	(*n* = 5)
Temp (°C)	39.7 ± 0.1	39.9 ± 0.1	39.8 ± 0.1#	40.1 ± 0.1	39.7 ± 0.1	40.3 ± 0.2
pH (units)	7.414 ± 0.030	7.447 ± 0.015	7.268 ± 0.069	7.444 ± 0.010	7.100 ± 0.042+	7.444 ± 0.005
$PaCO_2$ (mm Hg)	40.7 ± 2.7*	31.0 ± 1.2	68.9 ± 13.6#	32.4 ± 1.0	100.1 ± 12.7+	31.8 ± 0.9
PaO_2 (mm Hg)	363.2 ± 4.0*	412.2 ± 13.3	366.3 ± 4.9	400.6 ± 16.1	344.1 ± 14.3	410.6 ± 18.0
HCO_3^- (mEq/L)	24.8 ± 1.8	20.5 ± 1.0	28.4 ± 3.5	21.1 ± 0.7	28.0 ± 0.8+	20.7 ± 0.6
HR (bpm)	98 ± 9	111 ± 15	129 ± 18	102 ± 7	148 ± 29	116 ± 12
MAP (mm Hg)	133 ± 9	205 ± 29	110 ± 7#	151 ± 7	96 ± 4	147 ± 17
f (breaths/min)	8 ± 1	8 ± 1	17 ± 3#	8 ± 0	15 ± 3	9 ± 0
V_t (ml)	97 ± 4	—	67 ± 8	—	51 ± 11	—
V_{min} (L/min)	0.707 ± 0.048	—	1.021 ± 0.103	—	0.663 ± 0.121	—

Values are means ± SEM. The number of cranes at each multiple of MAC is shown in parentheses.

*$P \leq 0.05$ between data for spontaneous ventilation versus controlled ventilation at 1 × MAC.

#$P \leq 0.05$ between data for spontaneous ventilation versus controlled ventilation at 1.5 × MAC.

+$P \leq 0.05$ between data for spontaneous ventilation versus controlled ventilation at 2.0 × MAC.

Abbreviations: MAC = minimal anesthetic concentration; Temp = esophageal temperature; HCO_3 = bicarbonate; HR = heart rate; MAP = mean arterial blood pressure; f = respiratory frequency; V_t = tidal volume; V_{min} = minute ventilation.

Statistical Analysis

Circulatory and respiratory data at 1, 1.5, and 2.0 times the MAC during spontaneous and during controlled ventilation were compared using Student's *t*-test and a Bonferroni correction technique for multiple (3) comparisons. Student's paired *t*-test was used to test for a significant difference between data at a common multiple of the minimal anesthetic concentration during spontaneous and controlled ventilation. A level of $P \leq 0.05$ was considered statistically significant.

Results

The minimal anesthetic concentration for isoflurane during spontaneous ventilation was 1.34 ± 0.14 vol% (mean ± SD). The minimal anesthetic concentration was not redetermined during controlled ventilation. The minimal anesthetic concentration determined for each crane during spontaneous ventilation appeared to be valid for the controlled ventilation studies. If isoflurane concentration decreased slightly below the minimal anesthetic concentration in a particular crane during controlled ventilation, the bird would start to move.

Concentration-dependent respiratory depression during spontaneous breathing was evidenced in all cranes by an increase in $PaCO_2$ (Table 1). Due to isoflurane-induced apnea, dose-response data were collected from only 4 of the 6 cranes at 2 times the MAC during spontaneous ventilation. During spontaneous ventilation, mean respiratory rate increased significantly while tidal volume decreased significantly at 1.5 and 2.0 times the MAC when compared to values at 1.0 times the MAC (Fig. 1). Minute ventilation increased significantly at 1.5 MAC. With increasing concentrations of isoflurane, arterial blood pH progressively decreased during spontaneous ventilation as a result of respiratory acidosis. During spontaneous ventilation, tidal volume was highly variable in three of the six cranes. The breathing pattern was cyclic and characterized by several breaths of large tidal volume followed by several breaths of small tidal volume (Fig. 2). As the concentration of isoflurane was increased, the larger breaths were eliminated and mean tidal volume decreased. For purposes of data analysis, tidal volume was determined as the average of large and small breaths.

By controlling ventilation and maintaining $PaCO_2$ at a normal level the influence of carbon dioxide on selected physiologic variables could be determined (Fig. 3). Throughout controlled ventilation arterial blood pH never became acidic and bicarbonate remained constant at 20 to 21 mEq/L.

As the concentration of isoflurane was increased mean arterial blood pressure (MAP) decreased during both spontaneous and controlled ventilation (Fig. 4). However, blood pressure was significantly less depressed during controlled ventilation than during spontaneous ventilation at 1.5 times the MAC. Heart rate was variable but tended to be faster during spontaneous breathing than during controlled ventilation (Fig. 4).

A stage and plane of anesthesia suitable for intubation was achieved within 5 minutes from the start of anesthetic delivery. The duration of anesthesia during the spontaneous ventilation studies was 491 ±

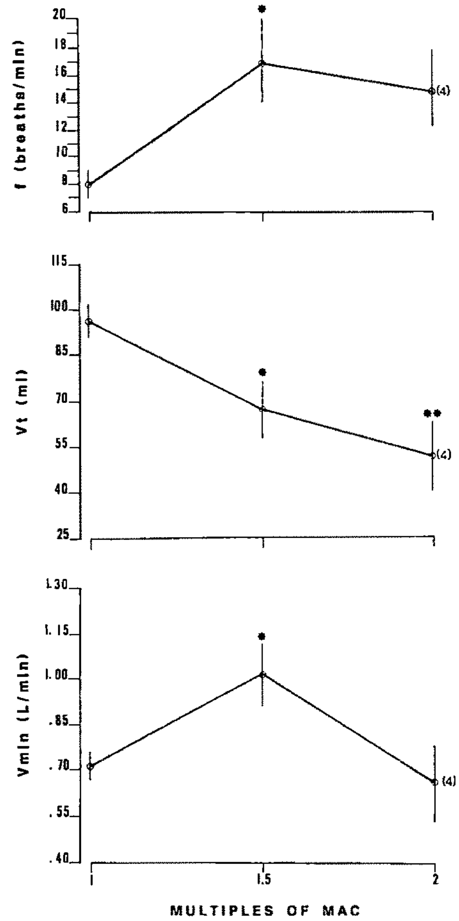

Figure 1. Effects of isoflurane on respiration in Sandhill cranes during spontaneous ventilation. The mean ± 1 SEM are indicated and the number of observations, if not 6, is indicated in parentheses. MAC = minimal anesthetic concentration. Significant differences ($P \leq 0.05$) between data are indicated by: * = 1.0 vs 1.5, ** = 1.0 vs 2.0.

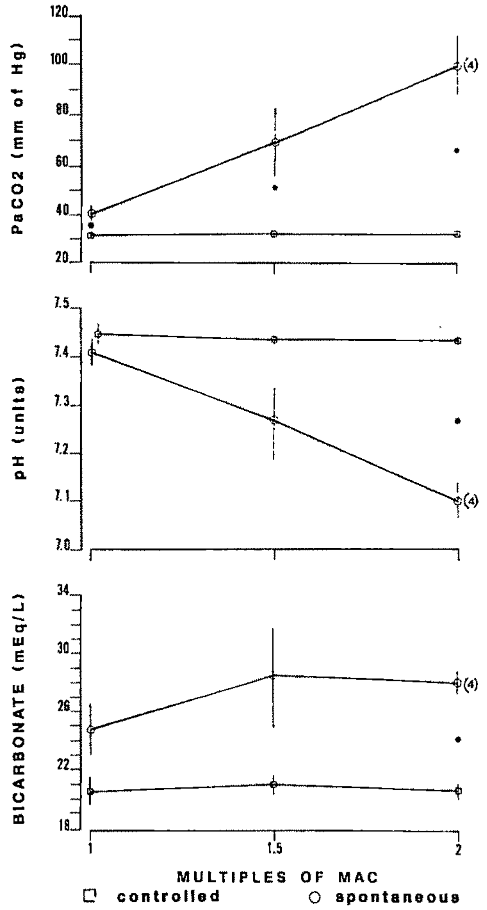

Figure 3. Effects of isoflurane on $PaCO_2$, pH, and bicarbonate in Sandhill cranes during spontaneous (0) and controlled ( ) ventilation. Data are mean ± 1 SEM. The number of observations during spontaneous ventilation, if not 6, is indicated in parentheses. The number of observations during controlled ventilation is 5. MAC = minimal anesthetic concentration. Significant differences ($P \leq 0.05$) between data at equipotent concentrations, are indicated by *.

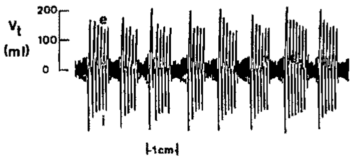

Figure 2. A typical tidal volume tracing recorded during spontaneous ventilation in one of three Sandhill cranes with a cyclic breathing pattern during anesthesia. The cycle consists of several breaths of large tidal volume followed by several breaths of small tidal volume. V_t = tidal volume in milliliters. e = expiration, i = inspiration. Paper speed = 0.01 mm/sec.

73 min with a recovery time to unassisted standing of 33 ± 9 min after anesthesia was discontinued. In the controlled ventilation studies the duration of anesthesia was 286 ± 40 min with the cranes standing unassisted within 26 ± 14 min after discontinuing anesthesia. One crane was euthanatized after the spontaneous ventilation study because of a fractured wing. The 5 remaining cranes survived both studies.

Discussion

In 1963, Merkel and Eger introduced the term MAC (minimum alveolar concentration) which was defined as the "minimal anesthetic concentration in the alveolus required to keep a dog from responding by gross purposeful movement to a painful stimulus" (4,5). Determination of MAC in animals is described as a "bracketing" technique since MAC is an anesthetic concentration midway between a concentration which allows and that which prevents movement following a noxious stimulus (4). In humans, because of the manner in which it is determined, MAC has been more narrowly defined as the minimum alveolar

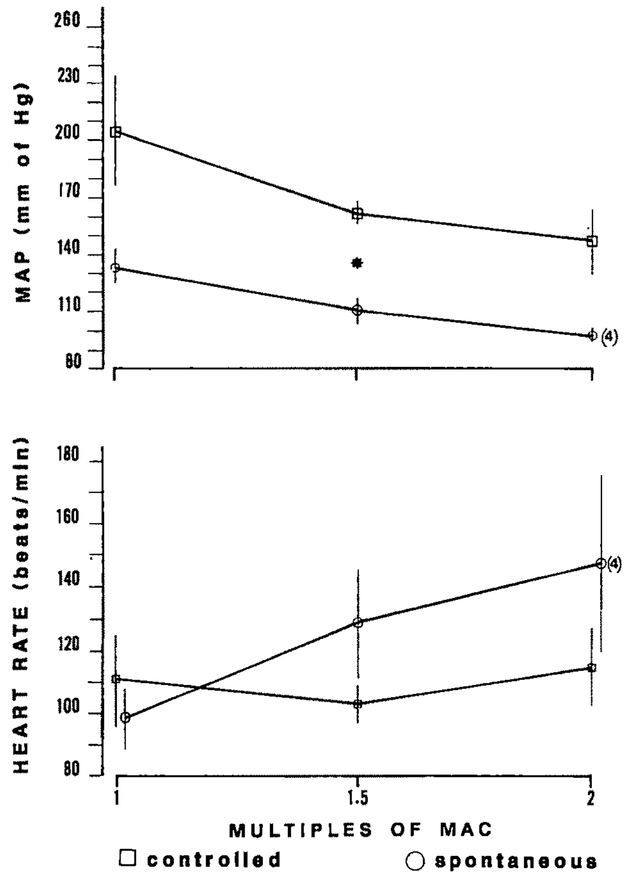

Figure 4. Effects of isoflurane on mean arterial blood pressure and heart rate in Sandhill cranes during spontaneous (0) and controlled ( ) ventilation. Data are mean ± 1 SEM. The number of observations during spontaneous ventilation, if not 6, is indicated in parentheses. The number of observations during controlled ventilation is 5. MAC = minimal anesthetic concentration. Significant differences ($P \leq 0.05$) between data at equipotent doses, are indicated by *.

concentration of an anesthetic which prevents movement in 50% of those patients exposed to a noxious stimulus (1). As a matter of convention the term MAC is used throughout this paper to describe the minimal anesthetic concentration determined in these cranes. However, we do not believe that MAC is an appropriate term for discussions regarding inhalation anesthesia in birds because it presupposes the presence of an alveolar lung. Birds have parabronchial lungs that differ morphologically and physiologically from mammalian lungs (6). On the other hand, to use a term such as ED50 implies an effective dose for an anesthetic that prevents movement or produces some measurable effect in 50% of a tested population (7,8); these terms also imply the use of log-probit analysis. We do not believe that these terms are appropriate since we determined the minimal anesthetic concentration using the "bracketing" technique.

The minimal anesthetic concentration of isoflurane for our cranes was 1.34 ± 0.14%. This is similar to MAC values for mammals such as the monkey (1.28 ± 0.18%), horse (1.31 ± 0.22%), rat (1.38 ± 0.06%), and dog (1.41 ± 0.16%) (9), and lends support to the observation that different species or classes of animals do not show large variations in effective concentrations for inhalation anesthetics (4).

An important issue is the rate of uptake of isoflurane in the cranes and the achievement of equilibration of isoflurane in the lungs with that in the arterial blood and brain. For the following reasons we believe that there was equilibration of isoflurane between the lungs, blood, and brains of our cranes during determinations of the minimal anesthetic concentrations and during the concentration-response studies. First, avian air sacs do not participate in gas exchange (10) and the rate of change of anesthetic concentration within the air sacs should be related to total gas volume and minute ventilation. Secondly, only 10% of the total volume of the avian respiratory system is located in the parabronchial lungs; this is considerably smaller than in mammals in which the fractional volume of gas in the gas-exchanging airways constitutes more than 95% of the total lung volume (11). Thus, birds do not have a large volume of gas in their lungs that can markedly slow the rate of change of gas concentrations within the lung. Thirdly, the avian lung has been shown to be a more efficient structure for gas exchange than the mammalian lung (11) and the uptake of an inhalation anesthetic should be as fast or even faster than in mammals. Finally, end-tidal isoflurane concentrations were held constant for a minimum of 15 minutes, a time that, in view of the above factors, should be sufficient to achieve anesthetic equilibration between lung, blood, and brain.

Increasing concentrations of isoflurane cause hypoventilation in humans, dogs, cats, and horses as evidenced by concentration-dependent increases in $PaCO_2$ (9,12,13). The relative effects of isoflurane on frequency and tidal volume depends on the species. Respiratory frequency is most depressed in dogs and horses; in cats, tidal volume (V_t) is the variable most depressed. In the cranes, unlike mammals, both frequency and tidal volume changed; frequency increased and tidal volume decreased as the concentration of isoflurane was increased. Minute ventilation remained essentially unchanged at 1 and 2 times the MAC and even increased significantly at 1.5 times the MAC. However, the overall net result was a decrease in effective parabronchial ventilation as evidenced by an increase in $PaCO_2$ at 1, 1.5, and 2 MAC. This decrease in effective parabronchial ventilation was pronounced at 2 times the MAC as evidenced by a mean $PaCO_2$ of 100 mm Hg which had a profound effect on blood pH and may have affected cardiovascular performance. The decrease in effective ventilation was due to an increase in deadspace ventilation (14). The cyclic variability in tidal volume observed in three of the cranes during spontaneous ventilation may be an additional manifestation of anesthetic-induced impairment of respiratory control mechanisms.

Isoflurane produces less cardiac depression and sensitization of the myocardium to catecholamines when compared to other inhalation anesthetics such as halothane (9,12,13). In this study we used ECG, heart rate, and blood pressure which is normally higher in birds than mammals (15), as indices of cardiovascular function. At no time during the spontaneous or the controlled ventilation studies did we observe or record any cardiac arrhythmias. There was a dose-dependent depression of mean arterial blood pressure which was more pronounced during spontaneous ventilation than during controlled ventilation. This differs from studies involving cats (12) and horses (13) anesthetized with isoflurane, in which mean arterial blood pressure was higher during spontaneous ventilation than during controlled ventilation. A blood pressure higher during spontaneous ventilation than during controlled ventilation has been attributed to two factors: the absence of adverse effects on the cardiovascular system attributable to positive pressure ventilation, and increased sympathetic stimulation due to elevated $PaCO_2$ in anesthetized animals during spontaneous ventilation (12,13). The methods in this study do not permit us to elucidate the possible mechanisms that may have contributed to the lower blood pressure observed during spontaneous ventilation.

In summary, the MAC for isoflurane in Sandhill cranes is similar to values for isoflurane MAC in mammals. In Sandhill cranes, isoflurane has concentration-dependent effects on cardiopulmonary function qualitatively similar to those observed in mammals. During anesthesia, controlled ventilation mitigated some of the adverse physiologic changes, such as hypercarbia and lower blood pressure, observed during spontaneous breathing.

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Clinical Reports

Oral Fiberoptic Intubation Over a Retrograde Guidewire

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Key Words: INTUBATION, TRACHEAL: fiberoptic, retrograde.

Tracheal intubation in patients with anatomical abnormalities of the head and neck requires superior skill and implementation of special intubation techniques. One of these special techniques is retrograde intubation.

Retrograde intubation, first described by Butler and Cirillo in 1960, is often used effectively in the most difficult of intubations (1). Fiberoptic bronchoscopy and intubation, described by Mulder et al., in 1975 (2), is also effective for intubation but requires skill, training and proficiency (3–5).

Retrograde intubation combined with fiberoptic bronchoscopic guidance can also facilitate intubation in patients with airway pathology. Retrograde fiberoptic intubation (RFI) is described sparingly in the literature. Our review of the literature revealed only one report of the clinical use of this technique (6). We describe use of RFI in several instances that represent challenging problems in airway management.

Case 1:

This patient was an 84-year-old man with a large squamous cell carcinoma of the mandible, that involved the lower lip and chin and extended to the buccal folds bilaterally. An operative resection was planned.

The absence of dysphagia, dyspnea or hoarseness suggested normal anatomy of the vocal cords. Past medical history included congestive heart failure treated with digoxin and lasix. Examination of the patient's airway revealed that an intubation, if performed in the usual manner, would obviously be difficult because of anatomical distortion of the oropharynx due to the tumor infiltration. RFI, therefore, was performed uneventfully in the operating room prior to the scheduled surgery.

Case 2:

This patient was a 54-year-old obese man scheduled for cervical laminectomy and vertebral body resection. He had a small mouth with prominent upper teeth, deviation of the nasal septum, and incomplete bilateral nasal obstruction. Because of the possibility of difficulty with standard laryngoscopy and intubation, an awake intubation was planned with neurological examination and awake positioning prior to the scheduled surgery.

His past medical history was negative. RFI was performed in the operating room prior to the neurological examination and positioning.

Case 3:

This patient was a 34-year-old obese woman, scheduled for lumboperitoneal shunt because of pseudotumor cerebri. Past medical history included well-controlled hypertension. More importantly, it was revealed that she had endured multiple failed attempts at orotracheal, blind nasotracheal and fiberoptic intubation just 1 week before. Because of the difficulty during prior intubation attempts, it was anticipated that RFI would be advisable. The patient readily agreed to the RFI because of her past unpleas-

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ant experience, and this was performed in the operating room.

Procedure

Our procedure for RFI was similar in all three cases. First, intravenous midazolam in varying dosages was given for amnesia and sedation. After oropharyngeal anesthesia was achieved with a 2% viscous lidocaine gargle and 2% aerosolized lidocaine, the neck was hyperextended (if not contraindicated) and the cricothyroid membrane (CTM) identified. This area was cleansed with an antiseptic solution and draped with sterile towels. One percent lidocaine provided analgesia of the skin over the CTM. Next followed transtracheal injection of 4 ml of 2% lidocaine through the CTM using an 18 g hypodermic needle, producing tracheal analgesia. The 18 g needle remained in place in the trachea at the CTM, with the bevel directed upward toward the vocal cords. A 125 cm., 0.025 cm. (#25) thick, Teflon-coated guidewire was then introduced through the needle in a cephalad direction through the vocal cords, up into the pharynx, and finally out through the mouth. The guidewire was then clamped at the skin at its point of entry through the skin and on through the CTM. The guidewire was then threaded through a 3.9 mm Olympus fiberoptic bronchoscope suction channel. The bronchoscope had already had a 7.0 mm endotracheal tube (ETT) threaded over its fiberoptic bundle and lodged into position at the proximal end of the scope. The bronchoscope was then gently guided into the mouth, retropharynx, through the cords, and down to the point of exit of the guidewire from the trachea at the CTM under direct visualization of the guidewire. As the bronchoscope was advanced further the Teflon guidewire was slackened at the exterior CTM insertion point. Tracheal placement of the bronchoscope was confirmed by visualization of tracheal rings and the carina. The guidewire was then unclamped at the CTM and removed via the proximal suction port of the bronchoscope. The ETT was then advanced gently down into the trachea. Correct placement of the ETT was confirmed by continuous visualization of the trachea and positioning of ETT above the carina. The bronchoscope was then removed. Correct placement of the ETT was further confirmed by capnography and by auscultation of bilateral breath sounds in the usual fashion.

Discussion

Retrograde fiberoptic intubation was first described by Lechman et al. in 1986 (6). This description was a team effort with retrograde introduction of the guidewire performed by the surgical team and concomitant fiberoptic bronchoscopy performed by the bronchoscopist. We found, however, that retrograde fiberoptic intubation is not only safe, but can be easily performed by one anesthesiologist without need for a team of surgeons and bronchoscopists. No problems or complications were encountered in any of our three cases reported here. Indeed, we found that direct visualization of the vocal cords with the help of a retrograde guidewire made this technique available to anesthesiologists with limited experience with fiberoptic endoscopy. Direct visualization also eliminates difficulties associated with blind advancement of an endotracheal tube over a guidewire, including trauma to soft tissues or entrapment of the tube in the pyriform fossa or valecula. The possibility of complications associated with puncture of the CTM appears to be remote. Casthely et al. (7), for example, performed blind retrograde intubation in 25 patients for open heart surgery. The only complication attributable to retrograde intubation was a small peritracheal hematoma in one patient that required no treatment. Akinyemi et al. (8) in reviewing complications of retrograde intubation in their series of 12 patients reported external bleeding of minor significance in three patients with breath holding and with respiratory obstruction in one each. Gold et al. (9) reviewed transtracheal anesthesia in 17,500 patients and reported two broken needles, two cases of laryngospasm, and four soft tissues neck infections. Not only is RFI safe; it eliminates problems that can be associated with blind nasal intubation or even with nasal fiberoptic bronchoscopic intubation. These include epistaxis, retropharyngeal dissection and abscess, and failure to intubate due to bleeding or unfamiliarity with the anatomy. The latter results in either cancellation of the case or tracheostomy.

The prudent anesthesiologist is today increasingly likely to be skilled in fiberoptic intubation. In the practice of anesthesiology, airway difficulties can occur at any time. The method described here allows a more rapid learning curve for the beginner of the technique of fiberoptic intubation and further avoids the unpleasant problems associated with nasal intubation, which, in the neophyte's hands, can in itself prove to be challenging.

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Preoxygenation in the Morbidly Obese: A Comparison of Two Techniques

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Key Words: COMPLICATIONS, obesity. VENTILATION, preoxygenation. OXYGEN, preoxygenation.

Morbid obesity by increasing acidity and volume of gastric contents, as well as by increasing and intragastric pressure (1), increases the risk of pulmonary aspiration of gastric contents during general anesthesia. Rapid sequence induction of anesthesia with cricoid pressure can prevent this complication. Gold et al. (2) have shown that four vital capacity breaths of 100% O_2 within 30 seconds elevates PaO_2 in non-obese patients as effectively as 5 min of tidal breathing of 100% O_2. Morbidly obese patients with altered lung volumes and diminished compliance, may respond differently to preoxygenation (3). We therefore compared two methods of preoxygenation in morbidly obese patients undergoing rapid sequence induction and intubation.

Methods

Thirteen morbidly obese patients (defined as more than 45 kg above ideal body weight) scheduled for gastric bypass surgery gave written informed consent and participated in this institutionally reviewed and approved study. No narcotic, benzodiazepine, or antisialogogue was administered preoperatively. Before induction of anesthesia, peripheral intravenous and radial artery catheters were inserted under local anesthesia. The patients were randomly assigned to one of two groups and breathed oxygen from a close-fitting face mask and a circle anesthesia system with a flow of 4 liters/min. One group, the 3-minute group (5 female, 1 male) breathed 100% oxygen at normal rates and with normal tidal volumes for 3 minutes while the other group, the 4 VC group (6 female, 1 male) took four vital capacity breaths of 100% O_2 within 30 seconds. Immediately following preoxygenation, we induced anesthesia with thiopental 4 mg/kg i.v. followed by succinylcholine 1 mg/kg i.v. to facilitate tracheal intubation. Samples for arterial blood gas tension measurement were obtained three times: 1) while spontaneously breathing room air prior to induction of anesthesia (baseline); 2) immediately after preoxygenation; and 3) immediately after intubation prior to initiation of manual controlled ventilation. If difficulty was encountered with intubation (i.e., more than 1 attempt was necessary) the patient was not included in the study. Blood samples were analyzed immediately on a Radiometer blood gas analyzer. Analysis of variance was used for statistical comparison. A p value < 0.05 was accepted as statistically significant.

Results

There were no intergroup differences between the groups in age, weight or height (Table 1), nor were there any differences in baseline blood gas tensions (Table 2). Both methods of preoxygenation resulted in similar increases in PaO_2 (Table 2). The 4 VC group had a significantly lower $PaCO_2$ and a tendency toward a higher pH (intergroup) following preoxygenation than did the 3-minute group (Table 2). After induction and intubation, $PaCO_2$ in the 4 VC group remained significantly less than that in the 3-minute group while the pH remained higher, though not statistically significantly so (intergroup) (Table 2).

When values were compared within the groups (i.e. intragroup), the pH did not change significantly at any time. The PaO_2 was significantly elevated after preoxygenation in both groups when compared to

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Table 1. Patient Demographics (Mean ± SD)

	3 Minutes (n = 6)	4 Vital Capacity (n = 7)
Age (yrs)	34.8 ± 11.1	37.6 ± 7.3
Weight (kg)	139.3 ± 18	135.7 ± 27.5
Height (cm)	64.8 ± 3.1	67.0 ± 2.9
Sex	5F 1M	6F 1M

Table 2. Arterial Blood Gas Tensions (Mean ± SD)

	3 Minutes (n = 6)	4 Vital Capacity (n = 7)	P (intergroup)
Baseline (Room Air)			
pH	7.38 ± 0.03	7.43 ± 0.04	NS
PaO_2 mmHg	87.4 ± 12.4	89.3 ± 13.5	NS
$PaCO_2$ mmHg	38.7 ± 5.6	36.2 ± 2.8	NS
%Sat	95.7 ± 1.7	96.3 ± 1.4	NS
After Preoxygenation			
pH	7.39 ± 0.04	7.43 ± 0.04	NS
PaO_2 mmHg	†425.4 ± 81.1	†397.5 ± 104.4	NS
$PaCO_2$ mmHg	41.0 ± 6.1	33.4 ± 2.7	<0.05
%Sat	99.5 ± 0.5	99.8 ± 0.1	NS
After Intubation			
pH	7.32 ± 0.03	7.37 ± 0.06	NS
PaO_2 mmHg	†337.2 ± 80.2	†314.00 ± 92.5	NS
$PaCO_2$ mmHG	*50.2 ± 6.0	*42.4 ± 6.06	<0.05
%Sat	99.3 ± 0.3	99.7 ± 0.2	<0.05

*$p < 0.05$ vs after oxygenation and baseline.
†$p < 0.05$ vs baseline.

baseline (room air) PaO_2 values. The $PaCO_2$ was significantly greater after intubation than after oxygenation in both groups ($p < 0.05$; Table 2). No other differences were seen.

Discussion

Anesthesiologists have long understood that significant arterial oxygen desaturation occurs following thiopental induction of anesthesia in patients who had been breathing room air (4). Dillon and Darsie recommended 5 minutes of oxygen administration before induction to avoid this problem (4). However, Hamilton and Eastwood demonstrated that 95% completion denitrogenation occurs within 2–3 minutes of tidal breathing of 100% O_2 using a circle system with four 1/min flows (5). Subsequently Gold et al. (2) demonstrated that preoxygenation with four maximally deep inspirations of 100% O_2 within 30 seconds increases PaO_2 as effectively as 5 minutes of tidal breathing of 100% O_2 in non-obese patients.

The morbidly obese patient has pulmonary dysfunction that may alter the response to preoxygenation, including increased inspiratory resistance and decreased dynamic compliance (6). These changes lead to uneven distribution of ventilation; arterial hypoxemia may develop (7). In addition, morbidly obese patients have a decrease in functional residual capacity, with airway closure occurring during tidal breathing (8–10). Continued perfusion of these unventilated alveoli further predisposes the morbidly obese patient to arterial hypoxemia.

Our data show that preoxygenation with 100% O_2 either for 3 minutes or with 4 VC breaths provides equal and adequate arterial oxygenation for rapid sequence induction of anesthesia and intubation in these patients. Similar results have been reported in non-obese patients (2) and parturients (11). Gambee et al. (12) and colleagues found that apneic patients developed desaturation more rapidly after preoxygenation with 4 VC breaths than did patients preoxygenated for 3 minutes. We did not maintain apnea until desaturation to 90% occurred; instead, once the endotracheal tube was inserted and the arterial blood sample was obtained the patients were ventilated. Although times between induction and intubation were not recorded, any patient with difficulty during intubation was eliminated from the study. Therefore we can make no conclusion concerning duration of apnea and desaturation. However, during the time required to secure the airway in these morbidly obese patients, oxygenation was similar with both techniques.

Morbidly obese patients have abnormal ventilatory responses to hypoxia and hypercarbia, including increased ventilatory responses to hypoxia but decreased responses to hypercarbia (13). The patients in our 3 min group hypoventilated significantly during preoxygenation and by the end of induction and intubation had developed a decrease in pH and significantly elevated $PaCO_2$. This hypoventilation was probably caused by a blunted ventilatory response to the CO_2 rebreathed from the dead space in the anesthesia face mask. This hypoventilation occurred in the absence of any narcotic premedication; obese patients premedicated with narcotics may suffer an even greater risk of hypoventilation. Hypoventilation did not occur in the 4 VC group; being encouraged to hyperventilate avoided the potential problems of a blunted CO_2 response.

We found that both 3 minutes of breathing 100% O_2 of 4 VC breaths of 100% O_2 within 30 seconds provide adequate and similar increases in $PaCO_2$ before induction of anesthesia in morbidly obese patients. However, patients in the 3-minute group developed slight CO_2 retention during preoxygenation; thus, the 4 VC technique may be more appropriate in this patient population.

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Can Epidural Fentanyl Control Autonomic Hyperreflexia in a Quadriplegic Parturient?

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Key Words: COMPLICATION—quadriplegia. SPINAL CORD—quadriplegia. ANESTHETIC TECHNIQUES—epidural.

In cord-damaged women of reproductive age, fertility, libido, sexual satisfaction, and bearing children are generally undiminished (1). Therefore, the association of parturition and paraplegia or quadriplegia is not rare and is increasing in incidence because of better medical care and rehabilitation. During parturition these patients may experience a life-threatening complication, namely autonomic hyperreflexia (AH) that includes severe hypertension and bradycardia associated with facial flushing, sweating, and pilomotor erection (1). This hypertensive crisis may lead to convulsions, cerebral hemorrhage (1), and even death (2). Various methods have been tried to block AH during labor and delivery by interrupting the reflex arc extending from the nociceptive site (the contracting uterus) to the final target (the cardiovascular system) by way of the spinal cord. One of the successful methods has been the epidural injection of meperidine (3). The rationale behind its use is the ability of narcotics to block noxious impulses at the posterior horn cells of the spinal cord of transected cat (4,5). However, meperidine also has local anesthetic effects in humans (6,7). After intrathecal injection of the drug, all the characteristics of spinal block including sensory and motor blockade are produced.

Epidural fentanyl used in association with obstetric anesthesia has been reported to improve the analgesic properties of bupivacaine during cesarean section especially during uterine incision, manipulation, and newborn extraction (8). Therefore, would fentanyl, a narcotic devoid of local anesthetic effects (9,10), be successful in controlling AH? This case report attempts to answer this question.

Case Report

A 30-year-old gravida-1, para O white female at 40 1/2-week gestation presented to the labor and delivery unit for perinatal management. The patient's pregnancy was uncomplicated. Past medical history revealed a C4-5 quadriplegia associated with AH due to an accident at 13 years of age. On the day of admission, the patient, while at home, experienced 10 to 15 episodes of AH manifested by severe headaches, blurred vision, tinitus, diaphoresis, and spasms of lower limbs. The symptoms, easily initiated by, e.g., moving the patient from the wheel chair to bed in the labor suite, resulted in a blood pressure (BP) of 220/120 mm Hg and a heart rate of 49 beats/minute from a baseline of 110/70 mm Hg and 68 beats/minute. We were consulted to see whether the AH could be controlled during the peripartum period. We decided to use epidural fentanyl first. The patient's cardiovascular and respiratory systems were closely monitored prior to injection of the epidural narcotic and for 24 hours thereafter with the use of an automatic oscillotonometric device (Dinamap) for BP, as well as an electrocardiograph (ECG) and a pulse oximeter. Decubitus ulcers were prevented with use of an Eggcrate® mattress, placing a pillow between the patient's knees and frequently moving her from side to side. Cervical dilation just prior to epidural injection of fentanyl was 1 cm and the uterine contractions were 5-8 minutes apart, with corresponding hypertension and bradycardia during the contractions (around 180/110 mm Hg and 55 beats/min). A 20-ga epidural catheter was inserted at L3-4 without difficulty. Seventy-five μg fentanyl in 10 ml preservative-free saline solution was injected epidurally. The patient's symptoms and vital signs responded favorably during and between uterine contractions with a stable BP and pulse, around 130/85 mm Hg and 80

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beats/min, respectively. At 38 minutes after epidural fentanyl injection, an oxytocin infusion was started to augment the uterine contractions. Ten minutes later, a fentanyl epidural infusion was begun at 10 μg/hour (1 μg fentanyl in 1 ml preservative-free normal saline solution at a rate of 10 ml/hour), followed in 14 minutes by artifical rupture of the fetal membranes. As a result of the cervical manipulations, although the patient did not experience any pain, she had an episode of AH lasting for several minutes with an increase in BP to 225/135 mm Hg and a decrease in pulse to 44 beats/min. Accordingly, it was decided to stop the fentanyl epidural infusion and to switch to an epidural local anesthetic. Fifteen milliliters of 0.25% bupivacaine was injected in 5-ml increments. Over 15 minutes, the BP gradually decreased to baseline levels at which time a continuous epidural infusion with the use of 0.125% bupivacaine (15 ml/hour) was started. From that point on, the cardiovascular system continued to be stable.

The fetal heart showed normal rate and variability even during the AH attacks. At 3 hours and 45 minutes from the start of epidural fentanyl, the cervix was completely dilated, and 20 minutes later a 7-lb 12-oz female was delivered with Apgar scores of 9 and 10 at 1 minutes and 5 minutes. The third stage of labor was completed without difficulty. The plan was to continue the epidural infusion of bupivacaine for 24 hours. However, 2 hours after delivery the catheter was removed because it became blocked. During the subsequent 12 hours, the patient had some fluctuations in BP with intermittent mild headaches followed by a smooth postpartum recovery. Arterial oxygen saturation during the monitored period (24 hours) was 92 to 99% on room air. She was discharged on the third postpartum day in a stable condition and without any manifestations of AH.

Discussion

For over a century, it has been known that the uterus has the capacity to contract normally in labor despite the severance of its nerve supply (11), including damage to the spinal cord above T10 due to trauma or disease. When the cord is completely severed, labor is painless but can be associated with AH. In fact, AH may be the only indication of onset of labor and, therefore, can be useful in predicting premature labor in quadriplegics (12). When the cord damage is incomplete, and spinal cord tracts only partially severed, labor can be unpleasant and associated with muscle spasms and ankle clonus. Anesthesia is, therefore, required for pain relief as well as control of AH in patients with complete or incomplete cord section during labor and delivery, and the anesthesiologist's role in controlling AH becomes very important. Proper understanding of the mechanism and the methods of control of AH is, therefore, essential in managing these patients' parturition.

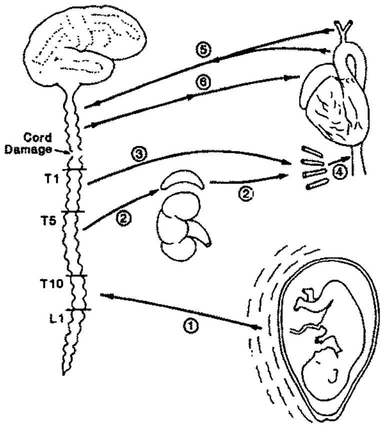

Figure 1. Mechanism of cardiovascular changes in automomic hyperreflexia. 1) Afferent impulses from contracting uterus to spinal cord segments T10-L1. 2) Efferent impulses from segments T5 to T9 to adrenal medulla causing discharge of catecholamines; 3) Efferent impulses from sympathetic centers T1-L1 directly to vascular bed causing vasoconstriction; 4) Increase in arterial blood measure as a result of stimuli by 2 and 3. 5) Afferent impulses from carotid sinus and aortic arch to cardiac centers in medulla oblongata; 6) Efferent impulses through vagus nerves to heart causing bradycardia.

The syndrome of AH is initiated by afferent impulses reaching the isolated spinal cord caudad to the level of the spinal cord damage. These impulses can result from noxious stimuli, including uterine contractions (Fig. 1). The response of spinal centers below the level of cord damage, and so uninhibited or modulated by the higher centers, is massive rather than specific, leading to extensive sympathetic stimulation of the cardiovascular system and of the neurologically isolated adrenal medulla (13). In addition, the denervated blood vessels are hypersensitive to sympathetic stimulation and to catecholamines released by the adrenal medulla. This leads to vasoconstriction in the denervated area and compensatory vasodilation in the innervated area. Therefore, a significant AH requires that the cord damage be above T6 to isolate the adrenal medulla (T5-T9) and a large proportion of the vascular bed. As a consequence of the extensive and marked vasoconstriction, hypertension occurs. Because spinal cord transection does not interfere with afferent connections of the baroreceptors from the carotid sinus and aortic arch to the cardiac centers in the medulla oblongata, reflex slowing of the heart usually occurs through the intact vagus nerves.

Various methods have been tried to control AH by interrupting the reflex arc at different levels extending from the origin of the noxious stimuli (the uterus) to the target site (the cardiovascular system). Delivery by cesarean section is associated with prompt cessation of AH. However, the abdominal route of delivery is reserved for obstetric indications only (1,11). These patients are capable of delivering vaginally; in some of these patients, as in our case, the second stage can be short despite the inability to bear down. The nociceptive impulses resulting from uterine contractions can be effectively blocked by paracervical block. However, the high incidence of fetal bradycardia and the possible fetal demise (14) makes such a technique inadvisable. Subarachnoid (15) and epidural anesthesia (16–18) have been successfully used to control AH by blocking the afferent nerves, the spinal neurons, and the efferent nerves. Subarachnoid block may cause a precipitous decrease in the arterial blood pressure (13,19), and labor may last longer than the effect of the block unless a continuous technique is employed. Therefore, epidural anesthesia is preferable. Vasodilator drugs that act either directly on the blood vessels or indirectly through the autonomic ganglia have been used to control AH, e.g., trimethaphan (20), sodium nitroprusside (18), or phentolamine (21). The most widely accepted technique to control AH is epidural analgesia, but the choice of a certain drug, its concentration, and its volume is controversial. An epidural narcotic also seem to be a good choice because it will interrupt the reflex arc by blocking the nociceptive impulses while sparing sympathetic tone that can be quite compromised by the cord damage. Previously meperidine succeeded in controlling AH (3), but in the present case fentanyl failed. Three reasons can explain this difference. First is the local anesthetic effect of meperidine. When meperidine is injected epidurally in a dosage of 100 mg, analgesia is produced without evidence of local anesthetic effect (22). However, when injected intrathecally in a dosage of 1 mg/kg, local anesthetic effects including motor and sensory blockage are evident (6,7). Absence of local anesthetic effects of meperidine in the epidural study is probably due to the limited amount of the drug in the CSF because movement of narcotics from the epidural space to the CSF across the dura may be restricted, and because of a partial loss of the epidurally injected drug through absorption by the rich vascular epidural plexus (7). Second is that the dose of epidural fentanyl administered before amniotomy might have been low (77.5 μg in 62 minutes). A higher dose could have been more effective but carries with it a greater risk of respiratory depression, a relatively more serious complication in a quadriplegic. Third is incomplete suppression by fentanyl of the visceral noxious stimuli. In the spinal-cord-transected cat, subarachnoid administration of fentanyl significantly suppresses the noxiously evoked activity of the wide-dynamic-range neurons located in the deeper laminae of the spinal dorsal horn (lamina V-type cells), mainly involved in somatic pain (23). However, the higher threshold superficial neurons of the posterior spinal cord horn (lamina I-type cells), mainly involved in visceral pain are more resistant to the suppressive action of fentanyl (24). Moreover, intrathecal fentanyl fails to improve natural endogenous analgesics in full-term pregnant rats (25). Therefore, in experimental animals, fentanyl does not completely block visceral nociceptive impulses. In humans, Carrie et al. (26) found that epidural fentanyl, up to a dose of 200 μg, was effective only in controlling early first stage labor pains, whereas failing in advanced first stage and second stage. Our case confirms both the previously mentioned experimental and human data because fentanyl was successful in obtunding AH effects of early uterine contractions but failed with the intense cervical stimulation of the amniotomy.

The objective manifestation in the form of AH in response to uterine contractions in a quadriplegic patient, as in our present patient, rather than pain in a healthy parturient, provided an opportunity to have a better study model for the efficacy of drugs in blocking the nociceptive impulses from the uterus. Our case report confirms that a predominantly mu-selective agent like fentanyl in not the narcotic of choice for controlling the visceral nociceptive impulses caused by uterine contractions. In future cases, predominantly a kappa-agonist drug such as nalbuphine (27) would be worthy of a trial.

The addition of bupivacaine completely suppressed AH. We arbitrarily administered the drug in the concentration and volume we usually use to control labor pains in normal individuals because it was impossible to determine the sensory level of the block by using a pinprick or an alcohol swab in our quadriplegic patient. However, at any time, the appearance of uncontrolled AH would have warranted increasing the dosage of the local anesthetic. For the intra- and postpartum control of AH, continuous epidural infusion was helpful in sustaining this effect.

The use of an epidural or subarachnoid narcotic carries the risk of respiratory depression, especially in a quadriplegic patient. The use of a pulse oximeter, or other means of closely monitoring the respiration, is essential.

In conclusion, this case of quadriplegic parturient gave us the opportunity to study the nociceptive impulses from uterine contractions and the efficacy of fentanyl in blocking these impulses at the spinal cord level without modulation from the higher centers.

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Electrical Localization of Spinal Roots for the Treatment of Spasticity by Intrathecal Alcohol Injection

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Key Words: ANESTHETIC TECHNIQUES—spinal, alcohol. ALCOHOL—subarachnoid.

Muscle spasticity is a common disorder after injury to the central nervous system often resulting in interference with patient positioning, decubital ulcer formation, and patient discomfort. Not infrequently, these patients also have concommitant medical problems complicating potential treatments or interventions. Anesthesiologists may be consulted in regard to neurolytic blocks in these complicated situations. The following case illustrates a patient with severe spasticity, complicated medical problems, and a unique approach to neurolysis.

Case Report

The patient was a 56-year-old male with a history of severe progressive cervical and lumbar spinal stenosis. Past surgical procedures included two cervical and lumbar laminectomies. Medical history included a long history of cigarette use with severe chronic obstructive pulmonary disease, necessitating the use of continuous oxygen therapy. Progressive spinal stenosis had left the patient an incomplete quadriparetic with no bowel, bladder, or erectile function. He had severe flexion spasticity of both hips and knees with the left side worse than the right. Spasticity in the hips was characterized both by an increase in muscle tone as well as by periodic clonic contractions. Difficulty with positioning had contributed to formation of a large sacral decubital ulcer that was not healing despite maximal medical care. A plastic surgeon felt the patient was a candidate for a musculocutaneous flap repair of the ulcer if better control of his spasticity could be obtained to prevent postoperative breakdown of the repair. The attending physiatrists felt that the patient's medical treatment of spasticity had been optimized, and referred the patient to our pain clinic for consultation and advice.

On examination, the patient was alert and cooperative, with severe emphysematous pulmonary changes requiring continuous oxygen by nasal cannula. The upper extremities showed only minimal weakness, whereas in his lower extremities the only voluntary muscle movement was the ability to slightly dorsiflex his feet. Distal to the tenth thoracic dermatome only patchy areas were sensitive to pinprick stimulation.

It was decided to perform an intrathecal spinal neurolytic block to decrease the spasticity in both hips. The technique was chosen to try to minimize positioning and procedure time in this patient with severe chronic obstructive pulmonary disease.

The patient was taken to the operating room, placed in the lateral position and, after the usual sterile preparation a 22-gauge Teflon-coated needle connected to a nerve stimulator was inserted at the L_{2-3} level using the paramedian approach on the superior side. The needle was advanced until cerebrospinal fluid was obtained. At that point the nerve stimulator was turned on and set to 2 mamps with a twitch rate of 1 Hz. The needle was manipulated in the subarachnoid space both by advancement and by lateral displacement until a strong flexion of the hip was obtained with 1 mamp. Absolute alcohol was then injected in 0.25 ml increments to a total of 1.0 ml. At approximately 0.75 ml of volume, hip flexion could no longer be obtained at even with 3.5 mamps. The patient remained in the lateral position for 20 minutes, was turned over, and the procedure repeated for the contralateral hip. Both 1 and 24 hours later there was marked reduction in spasticity of both hips with lesser reduction of knee spasticity. The neurolytic block was felt to be a success, and the

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Table 1. Review of Intrathecal Blocks for Spasticity

Investigator	Number of points	Agent	Satisfactory results (%)	Complications (%)
Liversedge and Maher 1960	32	5% phenol	16	9.3/3.1 transient/permanent bladder weakness
Nathan 1965	24	2–5% phenol	75	21 urinary function
Pederson and Juul-Jensen 1965	16	5–10% phenol	92.5	31 parathesia; 12.5 permanent bladder weakness

Satisfactory means the patient became more comfortable and less contracted.
From Wood (13).

patient eventually underwent a musculocutaneous flap repair of his decubital ulcer.

Discussion

In an intact nervous system, muscle tone is determined by a complex balance between three components: large alpha motor neurons in the anterior horn that supply motor input to muscle fibers; gamma neurons, also in the anterior horn that supply muscle spindle fibers; and descending spinal pathways that modulate activity in both alpha and gamma neurons (1). Gamma input activates alpha motor neurons with resulting maintenance of tone in the corresponding musculature while descending spinal pathways inhibit activity in both alpha and gamma neurons. With central nervous system injury, the loss of descending pathways allows uninhibited alpha and gamma activity with resulting spasticity (1).

Treatment of spasticity is directed at inhibiting or interrupting one of the above pathways. Medications such as baclofen (2) or benzodiazepines (3) chemically inhibit activity in alpha or gamma neurons, while clonidine has been used to decrease spasticity presumably due to alpha-2 receptor stimulation in the spinal cord (4). Surgical or neurolytic therapy attempts to interrupt the afferent or efferent components of the reflex loop. Recently, spinally administered morphine (5–7) or baclofen (8) and chronically implanted spinal cord stimulators (9–11) have been offered as an alternative form of spasticity therapy.

The use of neurolytic agents for the treatment of spasticity is a subject of numerous clinical trials and review articles (12–17). The agents most commonly used are alcohol or phenol, and the approach may be subarachnoid, subdural, epidural, paravertebral, or via motor points. All of the approaches have strengths and weaknesses that contribute to the mixed results in terms of efficacy, duration of successful results, as well as complication rate. An example of the diverse data in the literature on the effectiveness of intrathecal neurolytic blocks for spasticity has been compiled in a review article by Wood (13) and is shown in Table 1. Satisfactory results range from 16 to 92.5%, with a complication rate ranging from 3 to 31%. In general, with neurolytic blockade, as the success rate increases so do complications.

All described neurolytic block techniques have inherent problems both in localizing the level of the block and in determining the endpoint for the amount of neurolytic agent used while minimizing complications. With intrathecal or epidural blockade, even with radiographic control, it is difficult to localize specific nerve roots, and the amount of neurolytic agent recommended varies. In addition, the effectiveness of the block may not fully be evident until much later in the recovery room or ward, when the patient can be closely examined or stimulated. Paravertebral block, even with nerve stimulation, is often difficult and tedious, requiring multiple needle placements in patients with complicated anatomy and multiple medical problems. While peripheral nerve blocks offer the advantage of a more specific method of neurolysis, they may be associated with postblock dysesthesias.

The technique of intrathecal neurolysis is potentially advantageous in that it is easy to perform and requires only small amounts of neurolytic agent. However, in the cauda equina, individual spinal nerves cannot anatomically be located and so conventional intrathecal neurolysis utilizes small incremental injections in hopes of destroying the appropriate nerve roots while sparing others. The use of electrical stimulation to localize specific intrathecal nerve roots was first reported in canines by Sarnoff in 1950 (18). Since then, little has been written about this technique in humans. Our technique uses a stiff 22-gauge insulated needle with a stopcock to allow containment of fluid once the subarachnoid space is entered. We elected to use the paramedian approach, due to the difficulty in positioning the patient for a midline attempt and because the hypobaric alcohol could be injected near the superior nerve route of interest. Once in the subarachnoid space, the needle can be repositioned both in the anterior/posterior and in lateral directions, allowing more precise placement near the desired root. In addition, the spastic muscles that are the object of treatment can be stimulated, providing an endpoint in determining exactly where and how much of the agent need be injected. While the safety of this technique in completely intact humans has not been studied, the small current required and underlying neuropathology in patients with spasticity minimizes concerns.

In summary, a different approach to neurolysis is described using intrathecal nerve stimulation for precise needle location. Potential advantages include precise needle placement and the ability to electrically stimulate the muscles of interest. Whether this technique improves effectiveness or decreases complications remains to be studied.

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The Effect of Epidural Sufentanil on Shivering and Body Temperature in the Parturient

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Key Words: ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES—epidural. ANALGESICS—sufentanil. TEMPERATURE—shivering.

Temperature regulation is primarily controlled by the thermoregulating centers in the hypothalamus (1). Thermoreceptors in the skin and spinal cord provide afferent signals to the thalamus and hypothalamus. In addition, central thermoreceptors are sensitive to local core temperature. Stimulation of receptors in the anterior hypothalamus initiates anti-increase (in temperature) responses (vasodilation, sweating), whereas stimulation of the posterior hypothalamic receptors initiates the anti-decrease responses of vasoconstriction, epinephrine release, and shivering (2).

Narcotics alter body temperature in animals (3). Possible mechanisms for this include centrally mediated alteration of thermogenesis (4) and peripheral effects altering the distribution of and rate of change of body heat (5). We have observed in a preliminary report a decrease in body temperature and a reduction in shivering in postpartum patients who received epidural sufentanil after epidural lidocaine anesthesia for cesarean delivery (6). To determine the effect of different doses of epidural sufentanil on body temperature, we undertook a randomized double blind study in patients undergoing cesarean delivery.

Methods and Materials

This protocol was approved by the Committee for the Protection of Human Subjects from Research Risks of the Brigham and Women's Hospital, and written informed consent was obtained prior to entry into the study. Forty multiparous ASA physical status I patients undergoing elective repeat cesarean delivery were enrolled in the investigation. Prior to epidural catheter placement, an intravenous catheter was inserted, and 1500 ml lactated Ringer's solution was given (at room temperature 23–25°C). An epidural catheter was then inserted at the third lumbar interspace and directed cephalad. Sensory analgesia to the fourth thoracic dermatome was achieved with a room temperature solution of 2% lidocaine and 1/200,000 epinephrine. Patients were positioned supine on the operating table with a wedge beneath the right hip to maintain a pelvic tilt of 30°. Incremental doses of lidocaine with epinephrine were administered to maintain a T_4 sensory level during the operation.

After the procedure, the level of epidural anesthesia was allowed to recede until the patient complained of pain, defined by a pain score of three or greater on a 10 cm visual analogue scale with zero representing the absence of pain and ten representing the worst possible pain. At that point, we recorded the level of sensory anesthesia, degree of motor block, oral temperature, and the presence or absence of shivering. Sensory levels were determined by pinprick, and motor blockade was evaluated with the use of Bromage's criteria, in which degrees of motor blockade were classified in terms of the patient's ability to move the feet and legs (7). Patients were then, in double blind fashion, randomly given an epidural injection of 0, 25, 50, 75, or 100 μg of sufentanil either with or without 0.2 μg of epinephrine in a total volume of 10 ml normal saline solution. Following injection, oral temperatures and pain scores were again recorded, and the presence of shivering noted at half hourly intervals until discharge from the recovery room. Shivering was considered present when the patient noted it, and this

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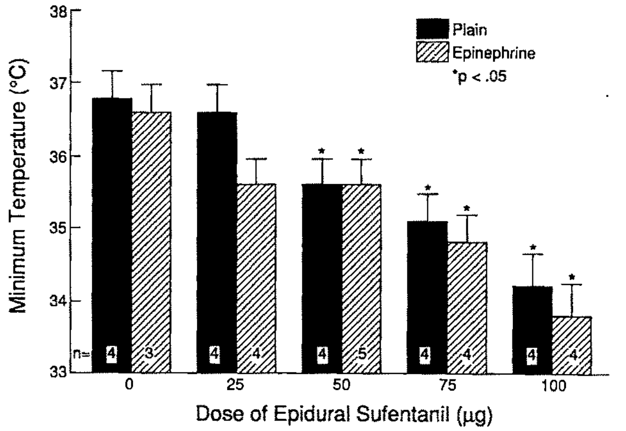

Figure 1. Lowest oral temperature (mean ± SD) recorded in patients given epidural injections of 10 ml of solutions with and without 0.2 μg epinephrine and with incrementally increasing doses of sufentanil from 0 to 100 μg. Number of patients in each group is indicated by the numbers at the base of each column. Asterisks (*) indicate those groups that vary significantly ($P < 0.5$) from the control group and among the dosage groups.

was confirmed by direct observation. The patients remained in the recovery room for approximately 2 hours until the usual recovery room discharge criteria were met.

Ambient operating room and recovery room temperatures were measured and recorded twice daily with the use of a standard mercury thermometer. The data were evaluated for statistical significance with the use of a two factor analysis of variance. Probability values of less than 0.05 were considered to be statistically significant.

Results

There were no significant differences in the height, weight, parity, or dose of local anesthetic among the groups. All patients arrived in the recovery room with oral temperatures (pre-sufentanil) between 35.8°C and 37.2°C without statistically significant differences among groups. Of the 10 groups, 8 consisted of four patients, the 0 μg sufentanil plus epinephrine group contained three patients, and the 50 μg sufentanil plus epinephrine group had five patients. Ambient room temperature was 23°–25°C over the course of the study.

With sufentanil doses of 50, 75, and 100 μg, there was a statistically significant decrease ($P < 0.05$) in body temperature as compared with doses of 0 and 25 μg (Fig. 1). At successively higher sufentanil doses, there was a significantly greater depression of temperature. Epinephrine was associated with a small but statistically significant decrease in body temperature independent of sufentanil. No shivering occurred in patients given 50 or more μg of sufentanil (Fig. 2). Sensory blockade lasted significantly longer when 75 and 100 μg of sufentanil were injected than it did in patients given no sufentanil (Fig. 3). Duration of sensory blockade with doses of sufentanil less than 75 μg was not statistically significantly different from that of the control groups. Motor blockade was not significantly different among any of the dosage groups.

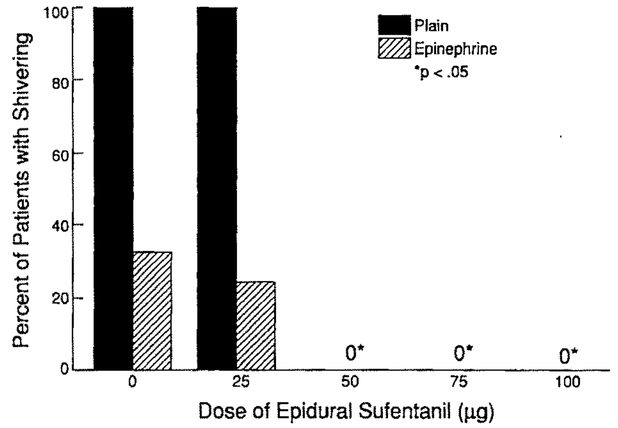

Figure 2. Relationship between dose of epidural sufentanil with and without 0.2 μg epinephrine and the percentage of patients with shivering. Asterisks (*) indicate those groups that vary significantly ($P < 0.05$) from the control groups.

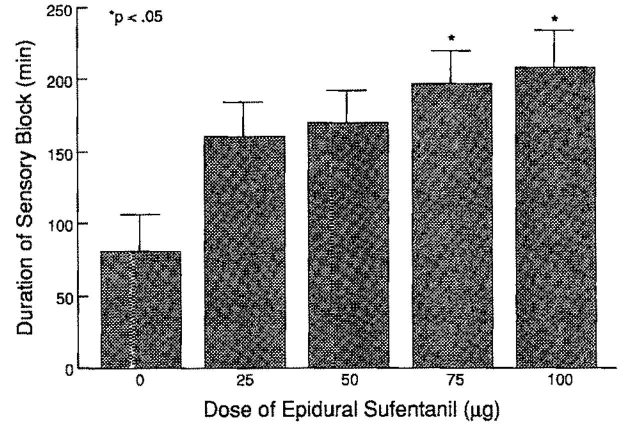

Figure 3. Duration of sensory blockade (min) (mean ± SD) when 10 ml of epidural solutions with incrementally increasing doses of sufentanil (0 to 100 μg) were injected following anesthesia. Asterisks (*) indicate those groups that vary significantly ($P < 0.05$) from the control group.

Discussion

In this study, we observed a dose related decrease in body temperature with increasing doses of sufentanil. In animals, the effects of narcotics on temperature are complex and species-dependent. Large parenteral doses of morphine, fentanyl, and meperidine can cause hypothermia in several species (1,3), as do small doses of intracerebral morphine (8). Further, low environmental temperatures accentuate the hypothermic effect. Low doses of narcotics produce hyperthermia and in thermoneutral or warm environment, hypothermic effects at higher doses are lost or, in some species, reversed, and hyperthermia occurs (3).

The thermic effect of morphine may result in part from a direct action on thermoregulatory centers in the hypothalamus (8). A direct action of narcotics on the spinal cord, altering "set point" and thus influencing temperature, has also been suggested (9). These effects are pharmacologically specific—i.e., antagonized by naloxone (10).

The patients in our study were all in a cool environment (23–25°C) and had received large doses of epidural sufentanil. Correlation has been shown between relative potency of agonists as analgesics and as hypothermic agents (3,11).

Sufentanil as an analgesic is approximately 8–10 times more potent than fentanyl and 1000 times more potent than morphine. Thus, it is not unexpected, in light of the relevant animal data, that patients in a moderate to low temperature environment receiving high doses of a highly potent narcotic would develop hypothermia.

A complicating factor in our patients is that the surgery required T_4 sensory levels and thus all patients had blockade of the majority of preganglionic sympathetic vasoconstrictor fibers (12). Although sensation was returning when the sufentanil was given, residual sensory blockage was present. Vasoconstriction as a thermoregulatory response to hypothermia therefore was lost. The patients may have had increased heat loss from the skin, although we did not assess this. The duration of sensory blockade was significantly greater as narcotic dose increased, perhaps contributing to the greater degree of hypothermia.

Another factor considered in our patients was the presence or absence of shivering. We observed that spontaneous shivering is decreased with increasing epidural sufentanil dosage. Shivering did not occur in any patient receiving 50, 75, or 100 μg sufentanil.

The mechanism for shivering frequently seen after epidural anesthesia has been examined by many investigators yet still remains unclear. Various mechanisms have been suggested; Ponte et al. (13) suggested that cold epidural anesthetic solutions have a direct effect on thermal receptors within the spinal canal. A differential block of warm and cold fibers might modify thermal input, resulting in inappropriate responses (14). Redistribution of body heat to the periphery secondary to vasodilatation produced by sympathetic blockade with resultant heat loss may also contribute to shivering. Use of room temperature intravenous fluid has been implicated (15). In the parturient, it has been suggested that shivering occurs secondary to maternal-fetal transfusion (16). Finally, Sessler et al. (17) suggest that tremors observed after general anesthesia are different electromyographically from shivering and may be secondary to a failed inhibition of spinal reflex arcs.

It has been demonstrated that morphine can reduce the discharge of neurons in lamina V of the dorsal horn (18) and may modulate shivering at this level. The action may also be at the hypothalamic level where narcotics modulate thermoregulation and an alteration in output at this level may inhibit shivering. The mechanism for shivering during epidural anesthesia therefore is unclear, as is the mechanism by which narcotics affect shivering, making difficult any explanation for why epidural sufentanil in large doses is associated with an absence of shivering even though smaller doses have no effect on the incidence of shivering.

In summary, in patients given lidocaine (with epinephrine) epidural anesthesia for cesarean delivery, we found that 50–100 μg epidural sufentanil given postoperatively was associated with a statistically significant decrease in oral temperature, whereas 25 μg epidural sufentanil had no effect on temperature. Patients who had decreases in temperature did not shiver. Further work is necessary to determine how sufentanil affects thermoregulation and shivering, to what extent other opiates affect thermoregulation in humans, and what role, if any, the absence of shivering plays in the development of hypothermia.

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Prolonged Vecuronium-Induced Neuromuscular Blockade in Children

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Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM.

Nondepolarizing neuromuscular blocking agents are known to have their effects potentiated by environmental and metabolic factors such as hypothermia, acute hypokalemia, hypermagnesemia, respiratory acidosis, and local anesthetics (1). Vecuronium is a nondepolarizing muscle relaxant developed in part for its intermediate duration of action. There are, however, case reports describing prolonged nondepolarizing neuromuscular blockade (NDNMB) in adults given vecuronium that have been attributed to concurrent use of antibiotics, cholestasis, neuromuscular disorders, or pregnancy (2–6). One case has been reported in which the cause or causes remain undetermined (7). We describe two cases of prolonged NDNMB while using vecuronium in children.

Case 1

A 6-year-old, 13-kg girl with spastic quadriplegia and cerebral palsy was scheduled to undergo bilateral medial release of the hips. Other past medical history and physical examination were unremarkable. Serum sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), and creatinine values were normal.

The patient received no premedication. An integrated evoked electromyograph (EMG) monitor (NMT 221, Puritan-Bennett Corporation, Wilmington, MA) was used to monitor NDNMB. Stimulation electrodes were placed over the distal median nerve, with recording electrodes placed on the thenar eminence to obtain an electromyograph of the abductor and flexor pollicis brevis muscles. Calibration of the EMG monitor was performed and resulted in a supramaximal electrical stimulus with a current of 60 mA and a pulse width of 100 μs during a 2 Hz train-of-four (TOF) every 20 seconds.

Anesthesia was induced with thiopental intravenously (IV) and isoflurane and N_2O by face mask, during which time the EMG monitor was calibrated and vecuronium 2.0 mg IV (150 μg/kg) was given to facilitate endotracheal intubation. Anesthesia was maintained with N_2O and isoflurane in oxygen. Inspired isoflurane concentrations averaged 1.2% and did not exceed 1.5%. Vital signs remained stable throughout the operation. The lowest level of esophageal temperature was 35.1°C. The only other medication given during the operative period was 150 mg of cefazolin IV 35 minutes after induction.

Electromyographic monitoring (Fig. 1) revealed a 25% recovery of T1 (first twitch of the TOF) at 1 hour; 50% recovery of T1 took approximately 2.5 hours. The inspired isoflurane concentration during this time ranged from 1.0 to 1.2%. Five hours after induction, the surgical procedure was finished; at this point, T1 was 65% of control and T4 was 82% of T1. Isoflurane (0.5% over the final 10 minutes) and N_2O were discontinued, and the patient's lungs were ventilated with 100% oxygen. About 5 minutes after discontinuation of inhaled anesthetics, T1 was 75% of control and T4 was 87% of T1. Administration of neostigmine (0.65 mg) with 0.2 mg/kg of atropine at this point increased T1 to 84% of control and T4 to 100% of T1. Twenty minutes after neostigmine was given, the patient's trachea was extubated and recovery was without incident.

Case 2

A 14-year-old, 45-kg boy with a sacral myelomeningocele was admitted for bladder surgery. Past medical history and physical examination were unremarkable except for a slightly decreased anal sphincter tone. Laboratory data (including serum levels of electrolytes and liver enzymes) revealed no significant abnormalities. Preoperative medication included oral cimetidine (300 mg), oral diazepam (5 mg), piperacillin (2 gm IV), and gentamicin (80 mg IV) 2

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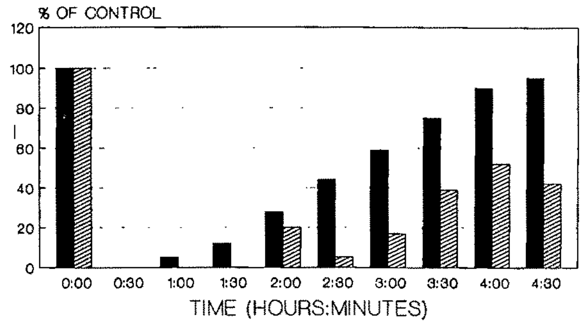
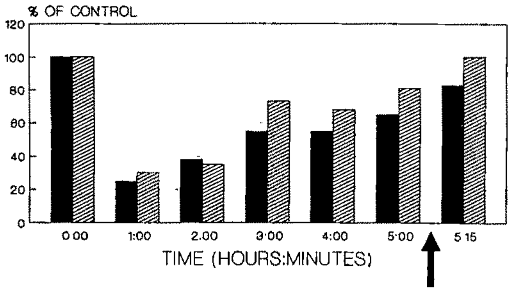


Figure 1. Electromyographic response from patient 1.



ARROW. NEOSTIGMINE (50 UG/KG) GIVEN

Figure 2. Electromyographic response from patient 2.

hours prior to surgery. An EMG monitor was placed on the patient's upper extremity, as in the previous case. Anesthetic induction (after atropine) included thiopental IV followed by isoflurane and N_2O in oxygen. The EMG monitor was then calibrated; a supramaximal stimulus was applied in the same manner as described in Case 1 except the stimulating current was 45 mA. Vecuronium (7.0 mg or 0.15 mg/kg IV) was then given, after which the patient's trachea was intubated without difficulty. Anesthesia was maintained with isoflurane and N_2O in oxygen.

Continued EMG monitoring (Fig. 2) revealed recovery of T1 to 25% of control at almost 2 hours. Recovery of T1 to 50% of control took 2 hours and 40 minutes. The inspired isoflurane concentration ranged from 1.2 to 1.5% during this time. The only other medication given in this period was piperacillin (2 g IV). Vital signs, arterial blood gas tensions, and serum electrolytes remained within normal limits. The lowest esophageal temperature was 35.3°C.

Approximately 4 hours and 45 minutes after induction, further relaxation was required (T1 was 100% of control) and additional vecuronium was given (2.5 mg or 55 μg/kg). This dose lasted 90 minutes. Thereafter, vecuronium was given in 1 mg (22 μg/kg) increments (total dose 9 mg); these doses resulted in an average of 45 minutes of blockade until a T1 of 25% of control was achieved. During the final 4 hours of the procedure, the inspired isoflurane concentration was 0.6 to 0.8%. The blockade was easily reversed with neostigmine at the end of the case, and the patient's trachea was extubated in the operating room. Recovery was without incident.

Discussion

We report two cases of prolonged vecuronium-associated NDNMB. For purposes of comparison, we examined the published studies of vecuronium pharmacokinetics in humans. Fisher and Miller (8) showed that a dose of 70 μg/kg in children produced an average duration of action (time until return of T1 to 90% of control) of 35 minutes and an average recovery index (time from 25 to 75% recovery of control T1) of 9.3 minutes. In a recent study in adults (9) that used the dose of vecuronium given to the children in our case reports (150 μg/kg), the average time to 25% recovery of control T1 was 41.4 minutes (9).

In our first case, we could find no unusual circumstances predisposing this patient to such a prolonged NDNMB. She received a cephalosporin, but cephalosporins do not affect NDNMB (10). The effect of isoflurane on the NDNMB in this patient was considered. Because we compared our data with published data obtained from children exposed to stable halothane concentrations (8), and since isoflurane and halothane have been found not to differ significantly in prolonging vecuronium-induced neuromuscular blockade at similar minimum alveolar concentration levels (11), we believe isoflurane had little to do with the prolonged NDNMB observed in this patient.

The second patient received two antibiotics that have been reported to prolong NDNMB to variable degrees (12). The longest times reported in adults for antibiotic-enhanced NDNMB with vecuronium (80 μg/kg) are 190 minutes (50% recovery) and 4 hours (by clinical estimates) (2,3). These values approximate the prolongation of NDNMB seen in our patient given antibiotics perioperatively.

Some of the penicillins have also been shown to increase the duration of NDNMB (10,12,13). The combination of piperacillin and gentamicin may account for some of the prolongation in blockade in our second patient. Many patients, on the other hand, received penicillins during NDNMB and do not develop clinically evident potentiation or prolongation of the effect of NDNMB.

Again, the effect of isoflurane was considered in this patient. As before, the anesthetic we administered to this patient was comparable with that given to patients in the study by Fisher and Miller (8).

Moreover, the duration of blockade from 50% twitch depression until 90% recovery in Case 2 was considerably prolonged compared with the duration of the same blockade interval measured by Rupp et al. (11) in patients given vecuronium and 1.8% end-tidal isoflurane (>2 hours vs. 24.3 minutes), although our patient was given a much lower concentration of isoflurane. Furthermore, these same investigators measured the duration of action (the time required to reach 90% recovery from a dose of vecuronium that provides 100% blockade of T1) in subjects given isoflurane (end-tidal concentration 0.71%). They found that this dose (19 μg/kg) produced a duration of action of approximately 26 minutes (11). In contrast, when 22 μg/kg of vecuronium was given to our second patient, the time until only 25% recovery averaged 45 minutes.

In conclusion, we report a case of markedly prolonged NDNMB following vecuronium in a child given normal doses of intravenous antibiotics and in a child in whom no cause could be determined.

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Minimal Effective Dose of Intrathecal Morphine for Pain Relief Following Transabdominal Hysterectomy

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Key Words: PAIN—postoperative. ANALGESICS—morphine. ANESTHETIC TECHNIQUES—SPINAL—morphine.

Intrathecal morphine is useful for relief of various types of pain. Postoperative pain relief is one of the most common indications (1). The dose range suggested for postoperative pain relief has ranged from 0.1 to 20 mg morphine (2–6), with the resulting pain relief lasting as much as 24 hours (7–10). Intrathecal morphine is also, however, accompanied by complications such as nausea, vomiting, urinary retention, pruritus, and delayed respiratory depression (11–15), the latter potentially life threatening (16). As side effects cannot be predicted (17) and because respiratory depression may be delayed by as much as 20 hours, careful observation for side effects is required (5,18,19). As a result, intrathecal morphine may not be as widely used as it deserves to be for postoperative pain relief because of lack of data on dose-response relationships for intrathecal morphine, in which responses included both delayed respiratory depression as well as potentially less lethal side effects.

In this study, we prospectively investigated the effects of low doses of intrathecal morphine, 0.10 mg as the maximum, on pain relief after transabdominal hysterectomy. We report the minimum effective intrathecal morphine dose defined as that amount of morphine that provides relief of postoperative pain with the least incidence of side effects.

Methods

One hundred eighty-eight ASA physical status I or II patients having transabdominal hysterectomies for myoma uteri between October 1984 and December 1987 in Mito Saiseikai General Hospital were studied with the use of a protocol approved by the hospital ethical research committee. Written informed consent was obtained from each patient. Patients given preoperative opiates or other analgesics, or having nausea or vomiting were excluded. The patients were divided into six groups at random according to the amount of intrathecal morphine given (Table 1).

Patients were premedicated with oral flunitrazepam 1.0 mg 90 minutes before entering the operating theater. Spinal anesthesia and intrathecal administration of morphine hydrochloride was performed as follows: the spinal mixture (total volume 2.2–2.8 ml) consisted of tetracaine hydrochloride 12–14 mg plus preservative-free morphine hydrochloride (0.00, 0.03, 0.04, 0.06, 0.08, or 0.10 mg) in 10% glucose. In the right lateral decubitus position, lumber tap was performed with use of a 23-gauge spinal needle at L_2–L_3 intervertebral space; the spinal mixture was injected at a rate of 0.2 ml/second and the patient turned to the supine position. Five minutes after the injection, the cephalad level of analgesia was T_4–T_6 by pinprick. Diazepam 10 mg was given intravenously as a sedative when necessary during the operation. Patients given analgesics or antiemetics intraoperatively, as well as those given antiemetics for nausea during the first 48-hour period after the intrathecal injection were excluded from the study.

For the first 48 hours after the intrathecal injection, the following observations and recordings were made by ward nurses who were not informed of the morphine doses: the time when analgesics were given for relief of incisional pain, whether the patient vomited or not, whether the patients complained of pruritus, and whether respiratory depression (respiratory rate

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Table 1. Patient Data (mean ± SD)

Group	I	II	III	IV	V	VI
Number	23	39	30	22	23	34
Morphine dose (mg)	0.00	0.03	0.04	0.06	0.08	0.10
Age (yr)	45 ± 7	45 ± 7	45 ± 8	45 ± 5	42 ± 6	43 ± 5
Height (cm)	154 ± 5	154 ± 6	152 ± 6	153 ± 4	155 ± 6	154 ± 5
Weight (kg)	56 ± 8	56 ± 10	54 ± 6	55 ± 4	56 ± 10	55 ± 9
Duration (hr)	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.2	1.5 ± 0.6	1.4 ± 0.4

No significant demographic differences in patients in the six groups. Duration = duration of surgery.

less than 10 respirations/minute or $PaCO_2$ >50 mm Hg) was observed or not. The incidence of urinary retention could not be evaluated because a urethral catheter was in place during and after surgery.

In patients who needed no analgesics during the first 24-hour period, pain relief was considered "effective" and, similarly, those who vomited in the first 48-hour period were labeled as "vomiting." The percentages of patients categorized as "effective" (in pain relief) and "vomiting" were calculated in each group.

Student's *t* test with the Bonferroni's correction was used for analysis of patient data. A chi-square test was used to evaluate the differences among the six groups for both "effective" and "vomiting." *P* values less than 0.05 were considered to be statistically significant.

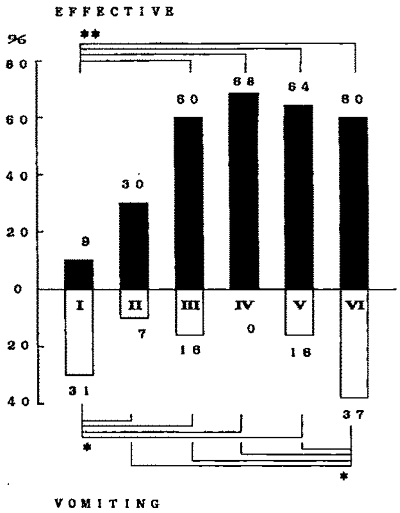

Figure 1. The percentages of patients listed as "effective" and "vomiting." **Significant difference, $P < 0.01$, *significant difference, $P < 0.05$.

Results

Seventeen patients were excluded from the study, 12 because they needed analgesics during their surgery and 5 because they were given antiemetics for nausea during the first 48-hour period. In the remaining 171 patients, there were no significant differences in mean age, height, weight, and operating time in the six groups.

Figure 1 shows the percentages of "effective" and "vomiting." The percentage of "effective" in groups III (0.04 mg), IV (0.06 mg), V (0.08 mg), and VI (0.10 mg) were significantly greater than group I (0.00 mg). There were no statistically significant differences between group I and II (0.03 mg) or among groups II, III, IV, V, and VI. The percentage of "vomiting" in groups I and VI was significantly greater than in groups II, III, IV, and V. There were no significant differences between group I and VI or among groups II, III, IV, and V. All 10 "vomiting" cases in Group I required analgesics, whereas 9 "effective" patients were included among the 13 "vomiting" patients in group VI. This difference was significant ($P < 0.01$).

Respiratory depression was not observed in any patient. Five patients complained of pruritus (3 "effective" in group II, 1 "effective" in group V, and 1 not "effective" in group VI). The relation between the dose and the incidence of itching was not significant.

Discussion

Among the previous reports on intrathecal administration of morphine for postoperative pain relief (2–4,11,12,17,20–24), the minimal intrathecal morphine dose was 0.25 mg (24). The side effects such as delayed respiratory depression, nausea, vomiting, urinary retention, and pruritus were often accompanied with doses as little as 0.25 mg (11,12). Differences in experimental design, methods, and characteristics of pain between previous reports and our study make comparisons of the present results with those of other studies difficult. However, the 0.04 mg dose used in the present study is smaller than those used in the previous reports. Recent reports indicate that the effective dose of epidurally administered morphine for the relief of postoperative pain ranges from 2–8 mg (20,25–27). No more than 2 (28) or 4% (29) of morphine epidurally administered is available in CSF, figures that agree with the present results.

The analgesic effect of intrathecal morphine is believed to be via opioid receptors in the spinal cord (8,30–32). On the other hand, nausea and respiratory depression are believed to be mediated via receptors in the brain stem (7,17,24,29) after redistribution of morphine to the brain stem following either systemic vascular absorption or rostal spread of morphine in the subarachnoid space toward the basal cistern (33,34). In this study, vomiting in group I was due to the surgery itself, whereas that in group VI represented a side effect of morphine. According to Sjöström et al. (17), 0.3 mg intrathecal morphine is believed to produce no pharmacologically significant plasma morphine concentration. On the contrary, our present results indicate that a 0.10 mg intrathecal dose of morphine, which was accompanied with a significant incidence of vomiting, represents overdose of opioid receptors in the spinal cord because the level of postoperative analgesia was not significantly different with 0.10 mg than it was with 0.04 mg. Also, limiting the intrathecal morphine dose made it possible in this study to produce analgesia without side effects such as vomiting and respiratory depression.

The lumbar intrathecal administration of a local anesthetic together with morphine has the advantage of providing simultaneously anesthesia for the operation and analgesia for the postoperative pain. In addition, intrathecal injection is technically easier and may be safer than epidural injection, especially in the thoracic region (8).

In conclusion, the intrathecal administration of morphine hydrochloride 0.04 mg to 0.08 mg mixed in hyperbaric tetracaine solution made postoperative systemic narcotics unnecessary in 60–70% of patients for 24 hours or more following transabdominal simple hysterectomy, and the incidence of adverse effects of morphine was minimal.

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Fifty-Eight Years Ago in
Anesthesia & Analgesia

B. Bolliger, K. Maddox: Experimental anesthesia with tri-brom-ethyl alcohol (Avertin) and sodium iso-amyl-ethyl-barbiturate (Amytal). Current Researches in Anesthesia and Analgesia: 1931;10:112–115.

These two anesthetists from Sydney, Australia, were as concerned in 1931 as other anesthetists and surgeons throughout the rest of the world by the constraints placed upon the practice of anesthesia when only inhalation and local anesthetics were available, especially since the two potent inhalation anesthetics, ether and chloroform, had so many manifest disadvantages. How much better it would be if anesthesia could be induced by getting a *non-volatile* CNS depressant into the blood. This could be and was accomplished by giving CNS depressants, even ether, rectally. This proved, however, to be more of a pharmacologic *tour de force* than a reliable, practical clinical technique. Ditto for intravenous injections of CNS depressants. Drugs available for intravenous injections at the time had extraordinarily long durations of action, amongst other disadvantages. Enter, then, both about the same time, two drugs for the induction of general anesthesia without putting a mask on the patient's face: tri-brom-ethanol in amylene hydrate (Avertin) for rectal administration, and a soluble form of a relatively short-acting barbiturate, Amytal, for intravenous injection. Amytal was the precursor of and soon to be displaced by an even more effective intravenous short-acting barbiturate: thiopental. Avertin continued, however, to be widely used for induction of anesthesia, especially in pediatrics and in uncontrolled and uncontrollable hyperthyroid states where surgery was the only treatment available. Eventually it became apparent that Avertin was, like chloroform, associated with a high incidence of hepatic damage, but Avertin was still being used until the late 1940s. That rectal Avertin and IV amobarbital represented significant advances in the early 1930s reflects very nicely indeed what the art and science of anesthesia consisted of at that time—and the challenges that anesthetists in the '30s faced that, fortunately, are no longer with us.

Effect of Oral and Intramuscular Famotidine on pH and Volume of Gastric Contents

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Key Words: GASTROINTESTINAL TRACT, STOMACH—pH and volume. HISTAMINE, FAMOTIDINE.

Since Mendelson's report in 1946 (1), there have been numerous reports of serious pneumonia associated with regurgitation and subsequent aspiration of gastric contents associated with anesthesia. It has been suggested that if the gastric pH is above 2.5 and the gastric content less than 25 ml, the pulmonary response to aspiration of gastric contents may be lessened in adults (2).

The H_2-receptor antagonists cimetidine and ranitidine are recent additions to the preanesthetic prophylaxis of the acid aspiration syndrome. However, 33% of patients given preanesthetic cimetidine have, nevertheless, been found to have a gastric pH lower than 2.5 (%). Short duration of action, potential adverse side effects, and the tendency to interact with other drugs also limit the routine use of cimetidine prophylactically. Ranitidine is more potent than cimetidine, has a longer duration of action, and is presumed to have minimal side effects, although hypotension has been reported with intravenous administration (3–6).

Famotidine, an amidine derivative is a new, potent, highly selective H_2-receptor antagonist. Its effects on hepatic blood flow, drug enzyme induction, and cholinesterase activity are negligible in comparison with those of other H_2-receptor antagonists (7–9). Also, unlike other H_2-receptor antagonists, famotidine has almost no adverse hemodynamic effects (10,11). Suppression of gastric secretion by famotidine continues for over 12 hours, which is adequate for postoperative prophylaxis of acid aspiration. However, preanesthetic administration of famotidine has been mentioned in only a few reports. Our study was designed to assess the effects of preoperatively administered oral and intramuscular famotidine on the pH and volume of gastric secretions immediately after and 1 and 2 hours after induction of anesthesia.

Patients and Methods

Ninety-two patients scheduled for elective surgery under general anesthesia were selected for study after their informed consent had been obtained. The study protocol had been approved by the Human Studies Committee of Osaka University Hospital. All patients were free of gastrointestinal disorders and were ASA physical status I-II. They were randomly allocated into three groups: Group A (N = 32), given 20 mg famotidine orally 2 hours before induction of anesthesia; Group B (N = 30), given 20 mg of famotidine intramuscularly 1 hour before induction; and Group C (N = 30), the controls given no famotidine. All patients fasted for a minimum of 8 hours before induction of anesthesia and were premedicated with 50 mg of hydroxyzine hydrochloride IM 1 hour prior to induction of anesthesia. Anesthesia was induced with 4 mg/kg thiopental with tracheal intubation facilitated by 1.5 mg/kg succinylcholine. Immediately after intubation a #18 French size Salem gastric tube was inserted. The position of the tube in the stomach was verified by auscultation of the epigastrium during insufflation of a few milliliters of air. The gastric contents were aspirated into a mucous trap by electric suction and by hand. Samples were obtained immediately after induction and 1 and 2 hours after induction.

The volume and pH of the aspirates were measured, the latter by means of a Merck Indicator paper, the accuracy of which had been confirmed. The data were statistically analyzed by either Student's *t*-test for unpaired data or the chi-square test. *P* values less

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Table 1. Criteria for Efficacy of Famotidine in Increasing pH and Decreasing Volume of Gastric Contents

Excellent	pH: 2.5 or higher and Gastric volume: 25.0 ml or less
Good	pH: 2.50 or higher and Gastric volume: 25.1 ml or more
Fair	pH: 2.49 or lower and Gastric volume: 25.0 ml or less
Poor	pH: 2.49 or lower and Gastric volume: 25.1 or more

Table 2. Patient Characteristics

Route of administration of famotidine	No. of patients	Sex: Male	Sex: Female	Mean age	Mean weight (kg)
Group A: oral	32	13	19	41.5	56.9
Group B: intramuscular	30	7	23	44.9	55.2
Group C: control	30	10	20	47.3	58.1
Total	92	30	62	44.5	56.8

No significant differences were observed.

Table 3. Gastric pH Over Time After Insertion of Gastric Tube (Mean ± SE)

	0 min		After 60 min		After 120 min	
	N	pH	N	pH	N	pH
Group A	32	6.2 ± 0.3*	28	6.4 ± 0.3*	16	7.2 ± 0.2*
Group B	26	5.7 ± 0.4*	26	6.0 ± 0.4*	17	6.7 ± 0.4*
Group C	30	2.7 ± 0.4	27	3.2 ± 0.5	20	3.6 ± 0.5

*$P < 0.05$ compared with Group C.
There were no significant differences between Groups A and B.

than 0.05 was considered statistically significant. The effects of famotidine on gastric pH and gastric volume during anesthesia were rated on a H-point scale from excellent to poor (Table 1).

Results

The three groups were similar in age and sex distribution (Table 2). As shown in Table 3, gastric pH was significantly higher in Groups A and B than in Group C at all three times. Volumes of gastric secretions were also significantly smaller in Groups A and B than in Group C at all three times (Table 4). There were no significant differences in gastric pH or gastric fluid volumes between Groups A and B at any time.

The number of "excellent" ratings (i.e., pH > 2.50 and gastric volume < 25.0 ml) was significantly greater in Groups A and B than in Group C (Tables 5–7).

Table 4. Changes in Gastric Volume Over Time Following Insertion of Gastric Tube (Mean ± SE)

	0 min		After 60 min		After 120 min	
	N	Gastric volume	N	Gastric volume	N	Gastric volume
Group A	32	8.7 ± 1.6*	31	5.1 ± 1.2*	20	4.2 ± 1.1*
Group B	30	8.0 ± 1.8*	29	3.6 ± 0.5*	23	2.2 ± 0.4*
Group C	30	21.9 ± 3.2	29	13.9 ± 2.4	21	8.7 ± 1.3

*Significantly different compared with control ($P < 0.05$).
No significant differences were observed between Groups A and B.

Table 5. Gastric Volume and pH Immediately After Insertion of Gastric Tube

	Group A	Group B	Group C
Excellent	30 (93.8)	26 (86.7)	8 (26.7)
Good	2 (6.3)	2 (6.7)	1 (3.3)
Fair	0 (0.0)	2 (6.7)	12 (40.0)
Poor	0 (0.0)	0 (0.0)	9 (30.0)
Total	32 (100.0)	30 (100.0)	30 (100.0)

Mann-Whitney *U*-test. Both famotidine-treated groups showed significantly higher levels than the control group ($P < 0.05$). No significant difference was observed between the two famotidine groups.

Table 6. Gastric Volume and pH 60 Minutes After Insertion of Gastric Tube

	Group A	Group B	Group C
Excellent	30 (96.8)	27 (93.1)	14 (48.3)
Good	1 (3.2)	0 (0.0)	0 (0.0)
Fair	0 (0.0)	2 (6.9)	11 (37.9)
Poor	0 (0.0)	0 (0.0)	4 (13.8)
Total	31 (100.0)	29 (100.0)	29 (100.0)

Mann-Whitney *U*-test. Both famotidine-treated groups showed significantly higher levels than the control group ($P < 0.01$). There was no significant difference between Group A and Group B famotidin administration.

Discussion

Regurgitation with subsequent pulmonary aspiration of gastric contents is a recognized hazard in anesthesia. Silent regurgitation of gastric contents is reported to occur in 4–26% of patients during general anesthe-

Table 7. Gastric Volume and pH 120 Minutes After Insertion of Gastric Tube

	Group A	Group B	Group C
Excellent	20	22	11
	(100.0)	(95.7)	(52.4)
Good	0	0	0
	(0.0)	(0.0)	(0.0)
Fair	0	1	10
	(0.0)	(4.3)	(47.6)
Poor	0	0	0
	(0.0)	(0.0)	(0.0)
Total	20	23	21
	(100.0)	(100.0)	(100.0)

Mann-Whitney *U*-test. Both famotidine groups showed significantly higher levels than the control group ($P < 0.01$). There was no significant difference between two famotidin groups.

sia, and about 10% of these patients are liable to aspirate the gastric contents. It is generally agreed that a gastric pH lower than 2.5 and a gastric volume of 25 ml are capable of producing severe pulmonary damage (2).

H_2-receptor antagonists are potent inhibitors of gastric acid secretion. This new, potent H_2-receptor antagonist, famotidine, appears to be more effective than cimetidine and ranitidine in the treatment of a variety of acid-peptic disorders and offers the advantage of prolonged preventive effect with presumably fewer side effects (12). In our control group, the mean gastric pH (2.7) and fluid volume (21.9 ml) were close to the minimum "safe" level immediately after the induction of anesthesia. Preanesthetic medication with oral or intramuscular famotidine, however, significantly increased the gastric pH and lowered the gastric volume. The mean gastric pH in the famotidine-treated groups was in the range of 5.7–7.2, which indicates that this drug effectively decreased gastric acid secretion. With the administration of famotidine, the level of gastric fluid volume was maintained below 10 ml throughout the study whereas in control patients the mean gastric volume was 8.7 ml 2 hours after induction of anesthesia.

A weakness of this and similar studies is that the exact position of the gastric tube at the time of aspiration of the gastric contents is not known. All gastric contents may not have been collected. The proportions of patients who had a gastric pH of >2.5 and a volume of <25 ml immediately after induction of anesthesia were 26.7% in Group C, 86.7% in Group B, and 93.8% in Group A. There were no cases in which famotidine-treated patients had a pH less than 2.5 and a volume more than 25 ml.

Oral famotidine was administered 2 hours prior to, and intramuscular famotidine 1 hour prior to, the induction of anesthesia. The depressant effect of famotidine on gastric secretion was observed immediately after the induction of anesthesia. With oral administration of famotidine the blood concentration reaches its maximum within hours; the half-life is 3.8 hours (13). In this study, we did not examine the effect of famotidine beyond 2 hours, but its suppression of gastric secretion is generally considered to last 12 hours (13,14). Thus, this drug appears to decrease the likelihood of aspiration pneumonia during and after general anesthesia.

We did not assess side effects in this study. However, blood pressure, heart rate, and electrocardiographic patterns reportedly remain unchanged after oral or intravenous administration of famotidine in single doses of up to 40 mg (8,10,11). Famotidine is generally considered not to interact with theophylline, warfarin, or other compounds metabolized by the lutein cytochrome P 450 enzyme system (8,15–18).

The present data demonstrate that oral or intramuscular famotidine before induction of anesthesia increased gastric pH and lowered gastric fluid volume to levels often regarded as safe and did so without adverse side effects.

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Letters to the Editor

Effects of Metaraminol on the Resistance and Capacitance Vessels in Humans

To the Editor:

During cardiopulmonary bypass (CPB), we have previously shown in patients undergoing open heart surgery that injection of ephedrine 30 mg into the venous reservoir of the Bentley oxygenator increased the mean perfusion pressure (MAP) by about 30%, but decreased rather than increased the reservoir volume (RV) by about 30%, suggesting a moderate increase of the peripheral resistance associated with venodilation (1).

The present report describes the peripheral vascular effects of metaraminol during CPB in 10 patients undergoing aortic and/or mitral valve replacement. Anesthesia was induced with diazepam 0.1 mg/kg, a mixture of alcuronium 0.25 mg/kg and pancuronium 0.1 mg/kg, and fentanyl 20 μg/kg. After orotracheal intubation, controlled ventilation was performed using 100% 0_2 and anesthesia was maintained with incremental doses of morphine amounting to 0.5 mg/kg. The pump oxygenator was primed with 1.5 liter of lactated ringers solution. The patients were perfused with a constant pump flow 2.3 $L/m^2/min$. After 10-20 minutes of CPB, a steady state of perfusion was reached. Metaraminol 2 mg was then injected into the venous line of the Bentley oxygenator and its effect on the MAP and RV monitored. Changes in MAP and RV were considered to reflect changes of the peripheral vascular resistance and venous capacitance respectively. The injection of metaraminol 2 mg was rapidly followed by a significant increase in the MAP to 125.5 ± 39.5 mmHg from 64.5 ± 13.2 mmHg, associated with an increase of the RV to 2950 ± 1066 ml from 2690 ± 1097 ml.

The results of the present report shows that metaraminol produces a marked increase of MAP associated with a moderate increase of RV. In contrast, ephedrine has been previously shown to produce in man a moderate increase of MAP associated with a decrease of RV (1).

Metaraminol has some direct effect on vascular smooth muscle, but its primary effect is due to release of endogenous norepinephrine, which exerts β-adrenergic effects on the heart and α-adrenergic action on the blood vessels (2,3). Thus, metaraminol acts on the peripheral vessels, similar to norepinephrine, as a selective α-adrenergic agonists which can constrict both the resistance and capacitance vessels, while ephedrine acts as a mixed α- and β-adrenergic agonist (2,3) which constricts the resistance vessels but dilates the capacitance vessels (1).

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Spinal Needles

To the Editor:

In 1987, we reported a problem with a new spinal needle (26 Gauge Spinocan by Burron Medical) (1). We noted clinical difficulty in detecting CSF drop formation in the hub during otherwise successful spinal anesthesia.

To investigate the problem, we measured the pressure-flow relationship for the needle in two ways, using lactated Ringers solution. Specifically, we measured the pressure required to provide a specific flow as well as the flow which resulted from a fixed applied pressure. We found the Becton Dickinson (BD) 26G spinal needle to have a resistance of 1.29 (± 0.21 SD) torr hr/ml while the Spinocan resistance was 2.70 (± 0.07).

We recently received samples of the re-designed Spinocan needle. We measured resistance using our constant-flow technique employing a pressure-monitoring infusion pump (IVAC 560). For the re-designed Spinocan, we found resistance to be 1.26 (± 0.4 SD) torr hr/ml. This is not different from the BD needle (p = .59, Student's *t* test).

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In summary, the re-designed Burron Spinocan thin-wall 26G spinal needle has a resistance to fluid flow indistinguishable from that of the BD 26G needle.

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Hypoventilation Caused by Ventilator Valve Rupture

To the Editor:

The report "Hypoventilation Caused by Ventilator Valve Rupture" by Sommer, et al. (Anesth Analg 1988;67: 999–1001) deserves comment. North American Dräger wishes to point out that the mushroom diaphragm of the Dräger AV Ventilator, which has been reported to have ruptured, has been used in 10,000 ventilators over the past 10 years. North American Dräger's records show no similar incident to the one reported in the above-referenced paper.

North American Dräger further wishes to state that the North American Dräger service manual contains a section which requires the inspection and service of the diaphragm during preventive maintenance service.

We agree with the author that only strict compliance with the manufacturer instructions for use, standard of medical care and use of modern monitoring equipment can prevent patient injury or death. Medical equipment is man made and therefore subject to failure or misuse. However practically no single fault condition will cause injury to a patient. The incident report contains a sequence of operator errors and one equipment failure which resulted in the potential for a patient injury. For educational purposes it appears beneficial to analyze the sequence of events during the reported incident.

First: The diaphragm of the valve was ruptured either as a result of age or incorrect handling. North American Dräger agrees with the authors that this condition existed prior to use.

Second: The equipment was not checked out prior to use. The checkout procedure recommended by North American Dräger or the one recommended by the F.D.A. (Federal Register/Volume 51 No. 60/Friday, March 28, 1986) would have revealed the ruptured diaphragm.

Third: The movement of the bellows was not observed. The instruction manual for the North American Dräger equipment requires that the bellows movement be observed to assure that the bellows travels between upper and lower stops.

Fourth: The volumeter that measures the exhaled tidal volume of the patient was not observed. In the event that the hypoventilation was as significant as stated in the report, there should have been a significant difference between the tidal volume adjustment at the ventilator and the reading at the volumeter.

Fifth: The peak ventilation pressure in the system was unusually low for the specific patient. When the operator adjusted the disconnect alarm to the unusual setting of 8cmH$_2$O, he should have been alerted and should have investigated the reason for the unusually low peak ventilation pressure.

Credit must be given to the team that investigated the cause of the problem after the ventilator alarm was initiated. The teams organized, and fast action obviously prevented a serious outcome for the patient, which would have been very difficult to defend.

Peter J. Schreiber, President
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In Response:

The authors appreciate the interest the manufacturer has taken in our case report. We agree that only in rare circumstances will a single equipment fault condition cause patient injury. As stated in both the case report and the manufacturer's comments, human error was required for the patient to be hypoventilated.

However, we wish to clarify a point the manufacturer has made. North American Dräger states ". . . [the] service manual contains a section which requires inspection and service of the diaphragm during preventive maintenance." Our comment (paragraph 6 of the discussion) pertained to the fact that ". . . the operating manual for this ventilator [not the service manual] contains no recommendation with regard to routine maintenance of this valve."(1) We therefore conclude that the valve is routinely serviced by the manufacturer, and that operators of this ventilator are not expected to carry out inspections or service of the valve.

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Nail Polish and Oximetry

To the Editor:

Coté and colleagues presented an interesting analysis of the effects of nail polish on measurements of oxygen saturation

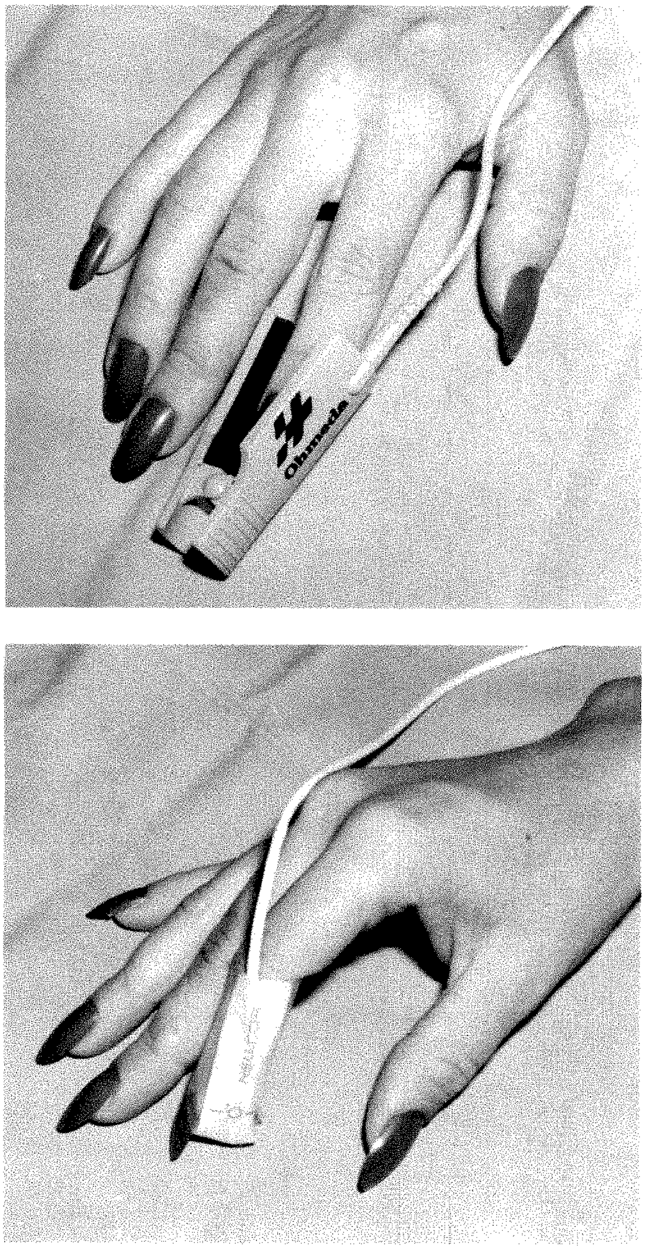

Figure 1. (A) Ohmeda reusable oximeter probe (#380-1000-042), and the (B) Nellcor disposable Oxisensor (digit oxygen transducer) probe applied in the lateral direction.

by pulse oximetry. (1) They demonstrated that certain types of nail polish (e.g. blue, green) interfered with oxygen saturation measurements. Consequently, they recommended that "nail polish should be removed routinely before pulse oximetry monitoring." As the authors suggested, outpatients often present for minor ambulatory surgical procedures with nail polish and its removal prior to application of an oximeter probe can inconvenience the patients and delay the start of anesthesia.

We have found that it is possible to avoid this problem by simply reorienting the probe so that it lies perpendicular to the fingernail (Fig. 1). In a study involving ten volunteers breathing room air, we compared pulse oximetry readings when the Ohmeda Biox 3740 pulse oximeter finger probe's light source and sensor was oriented through an unpolished nail and after reorienting the probe perpendicular to the nail surface. In addition, we repeated the measurements after covering the nail with various colored nail polishes or a metallic covering (that completely prevented light transmission through the nail). With uncovered nails, the oxygen saturation readings were the same (97 ± 1%, r = 0.99) whether the probe was oriented in an anterior-posterior or the lateral direction. As reported by Coté et al, with the probe oriented in the anterior-posterior direction, oximeter readings were lower or unobtainable with certain nail covering. However, the readings remained unchanged from the original values (97 ± 1%, r = 0.99) when the probe was reoriented in the lateral direction. Similar results were obtained with the Nellcor N200 (Model D-25) oximeter probe.

In summary, it is possible to avoid the effect of nail polish on pulse oximeter readings by reorienting the probe in the lateral direction on the finger tip. This simple maneuver can avoid the need for removing existing nail polish and artificial nail covers. In addition, this technique avoids difficulties which can be encountered when attempting to apply the probe to fingers with excessively long nails (Fig. 1B). Therefore, we would conclude that it is *not* necessary to remove all nail polish before application of a digital oximeter probe.

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The authors would like to thank their children (Kristine, Lisa, Chris, and Elizabeth) for volunteering to participate in this study.

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Book Reviews

Principles of Airway Management

Brendan T. Finucane and Albert H. Santora. Philadelphia: F. A. Davis Co., 1988, 277 pages, $19.95 (paper).

It is refreshing to discover a new monograph that is unpretentious, addresses an educational topic that is important and accomplishes the educational mission with simple efficiency. The basics of airway management is a skill that is generic to all physicians not only anesthesiologists. The burden of instruction for this fundamental topic will vary in different medical school curriculum, but will almost invariably be a part of an anesthesia medical student clerkship. This text will be an invaluable asset in the instruction of medical students and neophyte anesthetists.

To say that this text accomplishes its goal with simple efficiency is understating the quality of this educational material. The prose, as in a Hemingway novel, is unadorned and direct, yet it is incomparable. This text is immediately "user friendly." It is a paperback of 277 pages, has a cheerful green cover, lots of pictures, large print and bold section headings. Each chapter begins with a listing of the section headings. This simple technique emphasizes the structure and classification for the learner which makes it easier to retrieve and relate this new information. There are hardly any pages that have text alone, more often than not, there are illustrations, photographs, radiographs or charts on every page. The illustrations, photographs and radiographs are excellent quality and reinforce the adage that "a picture is worth a thousand words!" Tables and classifications are useful in classifying new material for the neophyte and promotes understanding and permits more efficient recall of material. Each chapter has references that not only reference articles, but have bibliography which lists pertinent texts for further reading for the student.

The pithy completeness and organization of this text are its strong points. There are some omissions, such as the Mallampati classification of the ease of intubation, but overall the work is comprehensive and current. Even new devices such as the Nu Trach cricothyroidotomy kit have been included. Experienced anesthesiologists will enjoy and learn by skimming this text. This monograph will become an important fundamental text in anesthesiology.

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Pediatric Anesthesia and Emergency Reference.

Meir Mazala, Mazala Medical Software, Cherry Hill, New Jersey, 1988, 1 disk, $40.00.

Accurate calculation of fluids and medications and selection of appropriate sized equipment is mandatory in the practice of pediatric anesthesia. Unlike managing the adult where errors are usually well tolerated, errors in small children are more likely to have serious consequences. This software for IBM and compatible computers was created in an attempt to reduce calculation errors. The program is simple to use, generates information quickly, and does not require that the operator have any computer knowledge other than how to turn the machine on and how to enter a few simple commands. The same software is available for use on a hand held Texas Instrument TI-74 computer with mini printer. The user is asked four questions whose answers are known in advance, i.e., patient weight, age, hematocrit and the history of prematurity. Using this information only, the program calculates intubation equipment, ventilation parameters, fluid requirements, allowable blood loss, and doses of anesthetic and resuscitative drugs. The literature that accompanies the disk indicates that the company will customize the program to fit the dosage specifications of the individual practitioner who purchases the same. The programmer's expectation is that a printout of this data will be generated which will accompany the child enabling health care professionals to refer to it prior to any intervention.

The program contains a warning that the calculations produced by the program should in no way eliminate the need for clinical judgment which would result in modification of the parameters or doses as the circumstances of the individual patient warrant. However, the program as it was configured for review generates a response to each variable for every patient. This reviewer is concerned that in inexperienced hands, most likely the principal users of this device, infants or critically ill children may receive a dose of a medication as listed on the printout which although appropriate for the patient's weight may not be appropriate for the child's age or physical status.

The program has limited application, if any, for anesthesiologists beyond those in training. It may find a place in non-operating room locations such as transport where a physician could review and modify the printout prior to departure to serve as a guide for nonphysician health care providers who are functioning autonomously.

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The Multidisciplinary Pain Center

J. N. Ghia, ed. Norwell, MA: Martinus Nijhoff Publishing, 1988, 185 pp, $67.50.

This book is part of a series, "Current Management of Pain," edited by Dr. Prithvi Raj with the intention of providing "up-to-date information on advances in the clinical management of acute and chronic pain, and related research as quickly as possible." This volume fulfills this goal in the field of multidisciplinary pain centers. The content is certainly up-to-date and a good source of information for all clinicians interested in the management of chronic pain, providing examples of different multidisciplinary approaches to a comprehensive treatment of the chronic pain patient.

The editor who directs the Anesthesia Pain Clinic and Diagnostic and Therapeutic Block services of the North Carolina Memorial Hospital, has chosen specialists in algology from not only his own discipline, but also from neurosurgery, psychiatry, and rehabilitation medicine and this contributes to this analysis of the multidisciplinary pain center. Bringing together different points of view and various approaches to chronic pain syndromes produces some controversies in the discussions, but emphasizes the multidisciplinary and even the interdisciplinary team approach rather than a traditional individual non-integrated treatment.

As in multi-author texts, there is some repetition. Although there is different perspectives and approaches by the various authors, there is overlap in the ultimate treatment approach to chronic pain syndromes. One area of agreement among different specialists is the importance of distinguishing between acute and chronic pain in both diagnostic and therapeutic maneuvers.

This book also highlights the important fact that chronic pain is a major public health issue and the direction into which the Pain Center movement will continue to evolve in this era of cost containment in the health care system. It also presents a good discussion of the accreditation and quality assurance processes put in place by the Commission on Accreditation of Rehabilitation Facilities (CARF) and ultimately tries to diffuse the confusion surrounding the organization and set-up of a truly comprehensive multidisciplinary Pain Center. This is especially important in view of the number of new Pain Centers opened recently. Thus, this book will provide valuable information to all interested in the functioning of the establishment of a multidisciplinary Pain Center whether they be "anesthesiologists, surgeons, other physicians, hospital administrators, nurses, pain managers, students, residents, and those concerned with health planning and health economics," as stated by Dr. Raj in his introduction to this useful book.

I would recommend this book to those interested in how to organize a truly multidisciplinary Pain Center as well as to those interested in referring patients to a Pain Center. It is a good starting point providing accurate and up-to-date information in the field and certainly easier than to scan the literature which is sparse and scattered in this area.

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The North American distributor for *Foundations of Obstetric Anesthesia* (314 pp, $39.50) edited by Barbara Morgan and published by Farrand Press of London (reviewed by Richard Banner, MD, in the December 1988 issue) is Sheridan House, Inc. of Dobbs Ferry, New York 10522.

Errata

Sukhani R, Winnie AP. Clinical Pharmacokinetics of Carbonated Local Anesthetics III: Interscalene Brachial Block Model. Vol. 68, No. 2, p. 90.

The authors wish to inform readers that a table tabulating supplemental blocks administered to patients was inadvertently omitted. Below is the table in its entirety:

Table 4. Patients Requiring Supplemental Blocks

Type of Block	Lidocaine HCl (n = 5)	Lidocaine CO_2 (n = 5)
Intercostobrachial (T_2)	5 (100%)	3 (60%)
Ulnar (C_8,T_1)	3 (60%)	2 (40%)

Urquhart ML, White PF. Comparison of Sedative Infusions During Regional Anesthesia—Methohexital, Etomidate, and Midazolam. Vol. 68, No. 3, p. 249.

The authors wish to inform readers that certain numbers appearing in Table 1 were incorrect. Below is the entire table with the correct numbers.

Table 1. Demographic Characteristics in Three Study Groups

	Midazolam	Methohexital	Etomidate
Number (*n*)	21	22	21
Age (yr; mean ± SD)	60 ± 15	55 ± 14	60 ± 18
Weight (kg; mean ± SD)	84 ± 11	79 ± 15	72 ± 18*
Outpatients (%)	27	41	43
Male (%)	95	91	67*
Prior anesthetics			
General (%)	90	73	90
Regional (%)	43	45	52
Regional technique			
Spinal (%)	100	86	81*
Epidural (%)	0	14	14
Axillary (%)	0	0	5
Time to initiate block (min)	14.0 ± 6	13.5 ± 4	14.4 ± 6
Highest Level† (dermatome) (mean ± SD)	T6 ± 2	T6 ± 2	T5 ± 3
Duration of operation (min; mean ± SD)	52 ± 26	79 ± 62	50 ± 38

*Significantly different from midazolam group, $P < 0.05$.
†With epidural and spinal anesthesia only.

Those wishing to order reprints of the above articles are advised that the corrections as listed will appear in the reprints.

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A Guide for Authors

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Nicholas M. Greene, MD
Editor in Chief
Anesthesia and Analgesia
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2. *Personal author(s) books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
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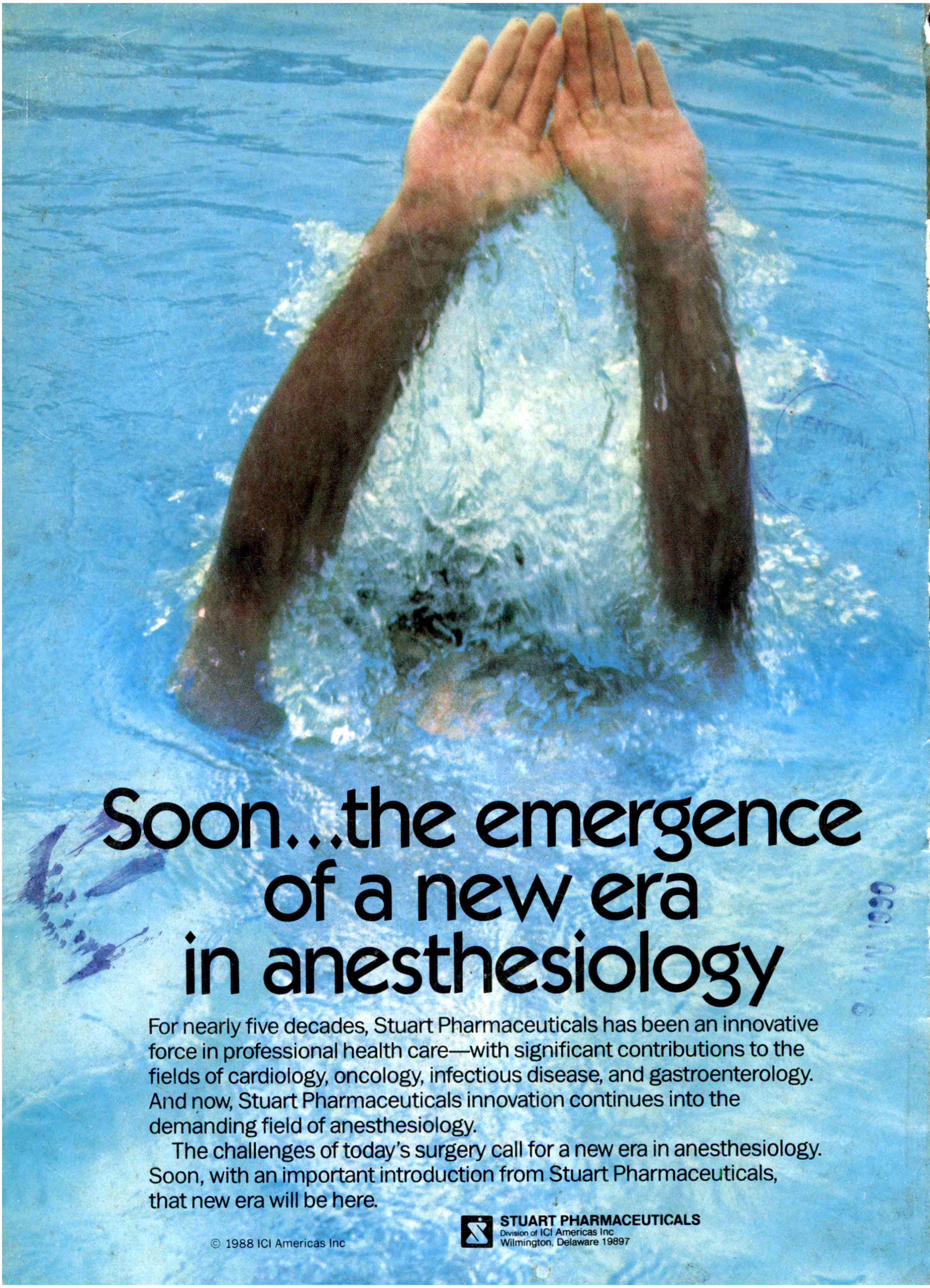
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